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(54) Title: POLYMER COMPOSITIONS WITH BIOACTIVE SILVER, COPPER OR ZINC COMPOUNDS, MEDICAL ARTICLES, AND PROCESSES

(57) Abstract: A polymer composition that includes a hydrophilic amine-containing polymer, an optional secondary organic polymer, an optional foaming agent, and a bioactive agent distributed therein, wherein the bioactive agent is selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof.

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POLYMER COMPOSITIONS WITH BIOACTIVE SILVER, COPPER OR ZINC COMPOUNDS, MEDICAL ARTICLES, AND PROCESSES

BACKGROUND

Polymer compositions that include bioactive agents (e.g., antimicrobial agents) are used for a variety of applications, particularly medical applications such as wound dressings and wound packing materials. Conventional antimicrobial agents include ionizable silver compounds (e.g., silver salts such as silver nitrate); however, they are typically not light stable and leave a stain on skin with which they come into contact. Thus, stable antimicrobial polymer compositions are desired.

SUMMARY

The present invention is directed to polymer compositions that include a bioactive agent (e.g., an antimicrobial agent). Such compositions are useful in medical articles, particularly wound dressings, wound packing materials, topical creams, and topical lotions, although a wide variety of other products can incorporate the polymer compositions. The bioactive agent is typically a silver compound, a copper compound, a zinc compound, or combinations thereof. Of these, it is more typically a silver compound. Such compositions are preferably stable. By this it is meant that the compositions are stable to at least one of the following types of radiation: visible light, ultraviolet light, electron beam, and gamma ray sterilization.

In one embodiment, the present invention provides a polymer composition preparable by a method that includes: combining components that include: an organic polymer; an inverse emulsion containing absorbent hydrophilic microparticles, which when in a substantially nonhydrated form have an average particle size of 10 microns or less, and wherein the microparticles include an amine-containing organic polymer selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof; a bioactive agent selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water; and an optional foaming agent; wherein the components are combined in a manner to produce a polymer composition wherein at least a portion of the bioactive agent is incorporated within the microparticles.

In another embodiment, the present invention provides a polymer composition that includes a hydrophilic amine-containing polymer having a weight average molecular weight of at least 1000 selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof, and a bioactive agent dispersed therein, wherein the bioactive agent is selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water.

Preferably, the polymer composition optionally includes a second organic polymer, thereby forming a mixture or blend of polymers. The second organic polymer is preferably a hydrophobic material. In one embodiment, the hydrophobic material forms a continuous matrix and the hydrophilic amine-containing polymer forms a discontinuous phase (e.g., microparticles). In another embodiment, the hydrophobic material forms a discontinuous phase and the hydrophilic amine-containing polymer forms a continuous matrix. In still another embodiment, the hydrophobic material forms a bi-continuous or co-continuous phase with the hydrophilic amine-containing polymer.

The present invention also provides medical articles that include the polymer compositions. The medical articles can be any of a wide variety of products, but preferably are wound dressings, wound packing materials, topical creams, or topical lotions.

In certain embodiments, the present invention provides a wound dressing that includes an apertured liquid permeable substrate and a nonadherent composition of the present invention.

The present invention also provides methods of making and using the polymer compositions.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably. Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides polymer compositions that include an amine-containing polymer, an optional second organic polymer, and a bioactive agent distributed therein. The polymer composition can be in a wide variety of forms, such as an extruded film (e.g., having a thickness of 0.5 millimeter (mm) to 10 mm), a coating, a foam, particles, a hydrocolloid (i.e., a material that contains particles dispersed in a second phase, typically, hydrophilic particles dispersed in a lipophilic phase), a gel, a lotion, a cream, a molded article, etc.

In certain embodiments, the hydrophilic amine-containing polymer is selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof. In certain embodiments, the hydrophilic amine-containing polymer is in the form of microparticles. The second organic polymer in certain embodiments forms a continuous matrix, and in certain embodiments is a hydrophobic material.

The bioactive agent is typically selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof. Of these, it is more typically a silver compound. In certain embodiments, the polymer composition is preparable from an organic polymer and an inverse emulsion that includes absorbent hydrophilic microparticles.

Such compositions are preferably stable. By this it is meant that the compositions are stable to at least one of the following types of radiation: visible light, ultraviolet light, electron beam, and gamma ray sterilization. Such compositions are useful in medical articles, particularly wound dressings, wound packing materials, topical creams, and topical lotions, although a wide variety of other products can incorporate the polymer compositions. The wound dressings can be used in their hydrated or swollen forms if desired.

In certain embodiments, the compositions of the present invention are nonadherent, although it should be understood that an adhesive (e.g., a pressure sensitive adhesive) could be added to an article that includes the composition. As used herein, the compositions of the present invention coated on a substrate display a 180° peel strength of less than 1 N/cm from steel according the to test procedure described in

the Examples Section. Preferably, the compositions of the present invention do not adhere significantly to wound tissue such that they do not cause pain and/or destruction of the wound tissue upon removal.

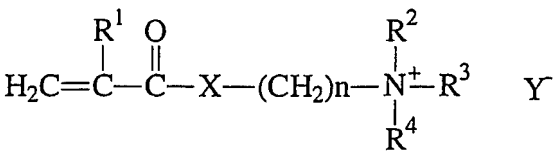
AMINE-CONTAINING POLYMER

The amine-containing organic polymer is selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof (including blends, mixtures, or copolymers thereof). Preferably, these are hydrophilic polymers (i.e., having an affinity for, absorbing, wetting smoothly with, tendency to combine with, or capable of dissolving in water).

Preferably, the amine-containing polymer has a weight average molecular weight of at least 1000. Examples include, but are not limited to, polyvinyl pyrrolidone, polyvinyl caprolactam, poly-N-vinylacetamide, poly-N-vinyl formamide, polyacrylamide, and the like.

Preferably, the amine-containing organic polymer includes a quaternary amine, and more preferably, the amine-containing polymer is a quaternary ammonium salt of an organic polymer. Such polymers are preferred typically because they can stabilize the bioactive compounds (particularly, silver compounds) effectively, they provide good release of the bioactive compounds, and they are absorbing of water or bodily fluids (e.g., wound exudate). Examples include, but are not limited to, polymerization products of cationic vinyl monomers as disclosed in EP 0 489 967 A1, and inherently antimicrobial quaternary amine polymers as described in U.S. Pat. No. 6,039,940.

Other suitable amine-containing polymers can be prepared from a quaternary ammonium monomer, which is a salt having an organo-ammonium group and a monoethylenically unsaturated group. For certain embodiments, the quaternary ammonium monomer has the following general Formula (I):



Formula (I)

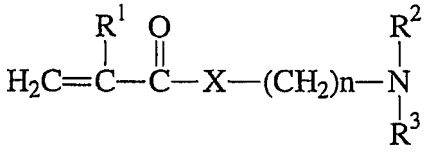
wherein: n is 2 to 10, preferably 2 to 3; R^1 is H or CH_3; R^2, R^3, and R^4 are each independently linear or branched organic groups, preferably having 1 to 16 carbon atoms (on average); X is O or NH; and Y^- is an acceptable anionic counterion to the N^+ of the quaternary ammonium group (e.g., one that does not adversely affect the polymerization of the monomers or antimicrobial activity of an added antimicrobial agent).

Preferably, R^2, R^3, and R^4 are each independently alkyl, aryl, alkaryl, or aralkyl groups. Alkyl groups are preferably lower alkyl, having 1 to 16 carbon atoms (on average) with methyl and ethyl groups being particularly preferred. Aryl is preferably phenyl but can be any suitable aromatic moiety such as those selected from the group consisting of phenyl, thiophenyl, naphthyl, biphenyl, pyridyl, pyrimidinyl, pyrazyl, pyridazinyl, furyl, thienyl, pyrryl, quinolinyl, bipyridyl, and the like. Representative of an aralkyl grouping is benzyl and representative of an alkaryl grouping is tolyl. X is preferably O. Representative counterions (Y^-) are Cl^-, Br^-, HSO_4^-, $CH_3CH_2OSO_3^-$, and $CH_3OSO_3^-$, with the chloride salts being particularly preferred. Alkyl groups can be straight or branched chain and alkyl and aryl groups can be substituted by non-interfering substituents that do not obstruct with the functionality of the polymers.

Useful copolymerizable quaternary ammonium monomers include, but are not limited to, those selected from 2-(meth)acryloxyethyl trialkyl ammonium halides and sulfates, and mixtures thereof. Examples of such compounds include, but are not limited to, 2-(meth)acryloxyethyl trimethyl ammonium chloride, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_3Cl$; 2-(meth)acryloxyethyl trimethyl ammonium methyl sulfate, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_3OSO_2OCH_3$; 2-(meth)acryloxyethyl methyl diethyl ammonium methyl sulfate, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)(C_2H_5)_2OSO_2OCH_3$; 2-(meth)acryloxyethyl dimethyl benzyl ammonium chloride, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_2(C_6H_5CH_2)Cl$ (all of the preceding monomers available from Ciba Specialty Chemicals, Woodbridge, NJ); 2-(methylacryloxy)ethyl dimethyl hexadecyl ammonium bromide, CH_2=$C(CH_3)CO_2CH_2CH_2N(CH_3)_2(C_{16}H_{33})Br$ (described in U.S. Pat. No. 5,437,932 (Ali et al.)); and the like. Various combinations of these monomers can be used if desired. Due to their availability, effectiveness in reinforcing (meth)acrylate polymers, and their antimicrobial activity, particularly preferred quaternary ammonium monomers are 2-acryloxyethyl trimethyl ammonium methyl chloride and 2-acryloxyethyl methyl

diethyl ammonium methyl chloride. Such monomers are typically hydrophilic. Various combinations of other monoethylenically unsaturated monomers that are reinforcing monomers can be used in the polymers of the present invention. Such reinforcing monomers include, but are not limited to, acrylic acid, methacrylic acid, ethylene vinyl acetate, and N,N-dimethylacrylamide.

As an alternative approach to providing polymers that contain a quaternary ammonium functional unit, it is possible to start with an amine monomer and form the quaternary ammonium unit following polymerization. For certain embodiments, the amine monomers have the following general Formula (II):



Formula (II)

wherein n, R^1, R^2, R^3, and X are the same as defined for Formula (I).

For certain embodiments, the amine-containing organic polymer (which is preferably in the form of microparticles) is absorbent (e.g., capable of absorbing water or bodily fluids). More preferably, the amine-containing organic polymer (which is preferably in the form of microparticles) is superabsorbent. In this context, "superabsorbent" means that the material will absorb at least 100% of its weight.

For certain embodiments, the amine-containing polymer is in the form of particles. If the amine-containing polymer is in the form of particles, it is typically in the form of microparticles. Preferably, the microparticles, when in a substantially nonhydrated form, have an average particle size of 10 microns or less, and more preferably, 1 micron or less. Typically and preferably, the microparticles have an average particle size of 0.5 micron or more when in a substantially nonhydrated form.

Preferred microparticles are as described in EP 172 724 A2 and EP 126 528 A2 made by reverse phase polymerization and have a dry particle size below 4 microns. The microparticles can be in an emulsion, such as an inverse emulsion that includes absorbent hydrophilic microparticles.

One type of inverse emulsion can be defined as a continuous hydrophobic liquid phase (e.g., mineral oil) and hydrophilic polymer particles dispersed within the hydrophobic liquid phase. Suitable examples of such materials are described in EP 0 126 528 A2. Such a material is commercially available under the trade designation SALCARE from Ciba Specialty Chemicals (High Point, NC). Suitable examples include SALCARE 95 and 96 which include a cationic homopolymer of the methyl chloride quaternary salt of 2-(dimethylamino)ethyl methacrylate (CAS No. 26161-33-1).

Other amine-containing polymers can be made from amine-containing monomers as described below and in EP 0 489 967 A1 and U.S. Pat. No. 6,039,940.

Monomers can be polymerized using techniques such as solution polymerization, emulsion polymerization, bulk polymerization, suspension polymerization, and the like. In particular, emulsion polymerization and suspension polymerization are preferable because the molecular weight of the polymer becomes high; solution polymerization is preferable because the molecular weight distribution is comparatively narrow; and bulk polymerization is favorable because no solvent is used.

In such polymerizations, initiators can be used to generate free-radicals upon the application of activating energy such as those conventionally used in the polymerization of ethylenically unsaturated monomers. Included among useful free-radical initiators are the thermally activated initiators such as organic peroxides, organic hydroperoxides, and azo-compounds. Representative examples of such initiators include, but are not limited to, benzoyl peroxide, tertiary-butyl perbenzoate, diisopropyl peroxydicarbonate, cumene hydroperoxide, azobis(isobutyronitrile), and the like. Generally, the thermal initiators are typically used in amounts from 0.01 to 5 percent by weight of monomer.

The polymerization of the polymer may also be initiated by photoinitiators. Such photochemically activated initiators are well known and have been described in the polymerization art; e.g., Chapter II of "Photochemistry" by Calvert and Pitts, John Wiley and Sons (1966) and in *Progress in Organic Coatings*, *13*, 123-150 (1985). Representative examples of such initiators include benzoin, benzoin methyl ether, benzoin isopropyl ether, benzoin isobutyl ether, and 2-hydroxy-2-methyl-1-phenyl-1-propane, benzildimethylketal and benzildiethylketal, 2-hydroxy-1-(4-(2-hydroxyethoxy)phenyl)-2-methyl-1-propanone. A presently preferred photoinitiator is

2-hydroxy-1-(4-(2-hydroxyethoxy)phenyl)-2-methyl-1-propanone. Generally, photoinitiators are used in amounts from 0.01 to 5 percent by weight of monomer.

The polymerization of the polymer may also be initiated by electromagnetic radiation such as electron beams and the gamma-rays of cobalt 60, and the like. The irradiation dose is typically between 1 and 100 kGy.

The polymer may be crosslinked by adding a crosslinking compound or through electron beam or gamma radiation. A crosslinking compound can be a multi-ethylenically unsaturated compound wherein the ethylenic groups are vinyl groups, allyl groups, and/or methallyl groups bonded to nitrogen or oxygen atoms. Exemplary compounds include divinyl, diallyl or dimethallyl esters (e.g., divinyl succinate, divinyl adipate, divinyl maleate, divinyl oxalate, divinyl malonate, divinyl glutarate, diallyl itaconate, diallyl maleate, diallyl fumarate, diallyl diglycolate, diallyl oxalate, diallyl adipate, diallyl succinate, diallyl azelate, diallyl malonate, diallyl glutarate, dimethallyl maleate, dimethallyl oxalate, dimethallyl malonate, dimethallyl succinate, dimethallyl glutarate, and dimethallyl adipate), divinyl, diallyl or dimethallyl ethers (e.g., diethyleneglycol divinyl ether, butanediol divinyl ether, ethylene glycol divinyl ether, ethylene glycol diallyl ether, diethylene glycol diallyl ether, butane diol diallyl ether, ethylene glycol dimethallyl ether, diethylene glycol dimethallyl ether, and butane diol dimethallyl ether), divinyl, diallyl or dimethallyl amides including bis(N-vinyl lactams), (e.g., 3,3'-ethylidene bis(N-vinyl-2-pyrrolidone)), and divinyl, diallyl or dimethallyl ureas.

Amine-containing polymers can be used in a variety of combinations. The total amount of amine-containing polymer(s) (e.g., microparticles) is preferably at least 1 percent by weight (wt-%), and more preferably, at least 5 wt-%, based on the total weight of the polymer composition. The total amount of amine-containing polymer(s) (e.g., microparticles) is preferably at most 60 percent by weight (wt-%), based on the total weight of the polymer composition.

BIOACTIVE AGENT

The polymer compositions of the present invention typically include a bioactive agent selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof. The silver, copper, and zinc compounds are typically in the form of salts. Preferably, the bioactive agent is a silver compound.

Preferably, at least the silver compound has a solubility in water of at least 0.1 gram per liter, and more preferably, the silver, copper, and zinc compounds each have a solubility in water of at least 0.1 gram per liter. Sufficient solubility is desirable such that the compounds are dissolved into the hydrophilic amine-containing polymer phase, although for certain embodiments silver, copper, and zinc compounds having lower solubilities can be tolerated as long as they are leachable. However, silver halide salts are undesirable because they are too insoluble.

Such compounds are typically antimicrobial, although they can also demonstrate other activities, such as antifungal activity. Examples include, but are not limited to, silver oxide, silver nitrate, silver acetate, silver lactate, silver sulfate, copper chloride, copper oxide, copper nitrate, copper acetate, copper lactate, copper sulfate, zinc chloride, zinc oxide, zinc nitrate, zinc acetate, zinc lactate, and zinc sulfate.

One or more bioactive agents of this type can be used. Herein, these are considered the primary bioactive agents. Optionally, one or more secondary bioactive agents (e.g., antimicrobial agents, antibiotics) can be used in combination with these primary bioactive agents. Preferred compositions have more than one bioactive agent.

The bioactive agent can be present in the polymer composition in an amount to produce a desired effect (e.g., antimicrobial effect). Preferably, the bioactive agent is present in an amount such that the polymer composition is stable. In this context, "stable" means the composition does not turn black over a typical exposure time in the presence of at least one of the following types of radiation: visible light, ultraviolet light, electron beam, and gamma ray sterilization.

A preferred molar ratio of the bioactive agent (e.g., silver compound) to amine-containing monomers (for the embodiments that prepare the polymer *in situ*) is at least 1 mole bioactive agent to 500 moles amine-containing monomer. Although there is essentially no upper limit, a preferred molar ratio is no more than 1 mole bioactive agent to 40 moles amine-containing monomer.

A preferred weight ratio of the bioactive agent (e.g., silver compound) to amine-containing polymers (for the embodiments that mix the bioactive agent with a previously prepared polymer) is at least 0.1 weight percent (more preferably at least 1 weight percent) bioactive agent based on the total weight of the amine-containing polymer. Although there is essentially no upper limit, a preferred weight ratio is no

more than 3 weight percent (more preferably no more than 2 weight percent) bioactive agent based on the total weight of the amine-containing polymer.

SECONDARY POLYMER

The polymer compositions can include one or more secondary organic polymers in addition to one or more amine-containing polymers. These can be liquids or solids at room temperature. This secondary polymer can by hydrophobic or hydrophilic, although preferably it is hydrophobic (i.e., antagonistic to, shedding, tending not to combine with, or incapable of dissolving in water).

Examples of hydrophilic materials include, but are not limited to, polysaccharides, polyethers, polyurethanes, polyacrylates, polyesters, and alginates. Examples of hydrophobic materials include, but are not limited to, polyisobutylene, polyethylene-propylene rubber, polyethylene-propylene diene-modified (EPDM) rubber, polyisoprene, styrene-isoprene-styrene, styrene-butadiene-styrene, styrene-ethylene-propylene-styrene, and styrene-ethylene-butylene-styrene. Hydrophobic materials are particularly desirable for nonadherent compositions and articles. Particularly preferred hydrophobic materials include styrene-isoprene-styrene and styrene-ethylene-butylene-styrene, and even more preferred materials include styrene-isoprene-styrene.

The secondary polymer can be in the form of a continuous matrix (i.e., phase) or a discontinuous matrix (e.g., in the form of particles). It can form a bi-continuous or co-continuous phase with the amine-containing polymer. The secondary organic polymer can be elastomeric, thermoplastic, or both.

Elastomeric polymers useful as optional secondary polymers in the invention are typically materials that form one phase at 21°C, have a glass transition temperature less than 0°C, and exhibit elastomeric properties. The elastomeric polymers include, but are not limited to, polyisoprenes, styrene-diene block copolymers, natural rubber, polyurethanes, polyether-block-amides, poly-alpha-olefins, (C1-C20) acrylic esters of meth(acrylic) acid, ethylene-octene copolymers, and combinations thereof. Elastomeric materials useful in the present invention include, for example, natural rubbers such as CV-60 (a controlled viscosity grade natural rubber having Mooney viscosity of 60 +/- 5 ML, 1+4 at 100°C, available as an International commodity); butyl rubbers, such as Exxon Butyl 268 available from Exxon Chemical Co., Houston, Texas;

synthetic poly-isoprenes such as CARIFLEX IR309, available from Kraton Polymers, Houston, Texas, and NATSYN 2210, available from Goodyear Tire and Rubber Co., Akron, Ohio; ethylene-propylenes; polybutadienes; polyisobutylenes such as VISTANEX MM L-80, available from Exxon Mobil Chemical Co.; and styrene-butadiene random copolymer rubbers such as AMERIPOL 1011A, available from BF Goodrich of Akron, Ohio.

Thermoplastic polymers useful as optional secondary polymers in the invention include, for example, polyolefins such as isotactic polypropylene; low density or linear low density polyethylene; medium density polyethylene; high density polyethylene; polybutylene; polyolefin copolymers or terpolymers, such as ethylene/propylene copolymer and blends thereof; ethylene-vinyl acetate copolymers such as ELVAX 260, available from E. I. DuPont de Nemours & Co., Wilmington, Delaware; ethylene acrylic acid copolymers; ethylene methacrylic acid copolymers such as SURLYN 1702, available from E. I. DuPont de Nemours & Co.; polymethylmethacrylate; polystyrene; ethylene vinyl alcohol; polyester; amorphous polyester; polyamides; fluorinated thermoplastics such a polyvinylidene fluoride; polytetrafluoroethylene; fluorinated ethylene/propylene copolymers; halogenated thermoplastics such as a chlorinated polyethylene; and combinations thereof. Other exemplary thermoplastic polymers are disclosed in International Publication No. WO 97/23577.

Thermoplastic elastomeric polymers useful as optional secondary polymers in the invention are typically materials that form at least two phases at 21°C, flow at a temperature greater than 50°C and exhibit elastomeric properties. Thermoplastic elastomeric materials useful in the present invention include, for example, linear, radial, star and tapered styrene-isoprene block copolymers such as KRATON D1107P, available from Kraton Polymers, and EUROPRENE SOL TE 9110, available from EniChem Elastomers Americas, Inc. Houston, Texas, linear styrene-(ethylene/butylene) block copolymers such as KRATON G1657 available from Kraton Polymers, linear styrene-(ethylene/propylene) block copolymers such as KRATON G1657X available from Kraton Polymers, styrene-isoprene-styrene block copolymers such as KRATON D1119P available from Kraton Polymers, linear, radial, and star styrene-butadiene block copolymers such as KRATON D1118X, available from Kraton Polymers, and EUROPRENE SOL TE 6205 available from EniChem Elastomers Americas, Inc., polyetheresters such as HYTREL G3548, available from E. I. DuPont de Nemours &

Co., and poly-alpha-olefin based thermoplastic elastomeric materials such as those represented by the formula -(CH_2-CHR) where R is an alkyl group containing 2 to 10 carbon atoms and poly-alpha-olefins based on metallocene catalysis such as ENGAGE EG8200, an ethylene/l-octene copolymer available from DuPont Dow Elastomers Co., Wilmington, Delaware. Other exemplary thermoplastic elastomers are disclosed in International Publication No. WO 96/25469.

Various combinations of secondary organic polymers in various amounts can be used to produce desired effects. This can be readily determined by one of skill in the art based on the teachings herein.

OPTIONAL ADDITIVES

The polymer compositions of the present invention can include a wide variety of optional additives. Examples include, but are not limited to, secondary bioactive agents, secondary absorbent particles, foaming agents, swelling agents, fillers, pigments, dyes, plasticizers (for example, mineral oil and petrolatum), tackifiers, crosslinking agents, stabilizers, compatibilizers, extruding aids, chain transfer agents, and combinations thereof.

In addition to the bioactive agents described above (e.g., silver, copper, and zinc compounds), other (secondary) bioactive agents can be incorporated into the polymer compositions of the present invention. Examples include, but are not limited to, antimicrobial agents such as parachlorometaxylenol, chlorhexidine and salts thereof, iodine, and iodophores, and antibiotics such as neomycin, bacitracin, and polymyxin B. Preferred compositions have more than one bioactive agent.

In certain embodiments, polymer compositions of the present invention can include secondary absorbent particles. Such secondary particles have an average particle size of greater than 10 microns when in a substantially nonhydrated form. Preferably, such particles are superabsorbent. Examples include, but are not limited to, those described in U.S. Pat. No. 5,369,155.

In certain embodiments, polymer compositions of the present invention can include a foaming agent. The foaming agent can be a chemical foaming agent or a physical foaming agent such as those disclosed in International Publication No. WO 00/74916 and in U.S. Pat. Nos. 6,103,152, 5,476,712, and 6,284,362. Of these foaming agents, the thermally expandable microspheres described in U.S. Pat. No. 6,103,152 are

desirable for certain embodiments. Use of such thermally expandable microspheres in absorbent articles is further described in Applicants' Assignee's Copending Application Serial No. 10/387,263, filed March 12, 2003.

In certain embodiments, polymer compositions of the present invention can include a swelling agent, preferably a nonvolatile swelling agent. Examples of swelling agents include, but are not limited to, polyols, monosaccharides, ether alcohols, and combinations thereof. Specific examples are disclosed in U.S. Pat. No. 5,270,358.

In certain embodiments, polymer compositions of the present invention can include fillers, which can be inorganic or organic. Examples of inorganic fillers include, but are not limited to, barytes, chalk, gypsum, kieserite, sodium carbonate, titanium dioxide, cerium oxide, silica dioxide, kaolin, carbon black, and hollow glass microbeads. Examples of organic fillers include, but are not limited to, powders based on polystyrene, polyvinyl chloride, urea-formaldehyde, and polyethylene. The fillers may be in the form of fibers, such as chopped fibers. Examples of suitable chopped fibers include glass fibers (typically 0.1 millimeter (mm) to 1 mm long) or fibers of organic origin such as, for example, polyester or polyamide fibers.

In order to confer color to the polymer compositions it is possible to use dyes or colored pigments of an organic or inorganic basis such as, for example, iron oxide or chromium oxide pigments or phthalocyanine- or monoazo-based pigments.

METHODS OF PREPARATION OF POLYMER COMPOSITIONS AND ARTICLES

Whether, starting with monomers and polymerizing the monomers in the presence of the bioactive agent, or adding a bioactive agent to a previously prepared polymer, the components are combined in a manner to produce a polymer composition having a bioactive agent dispersed therein.

For certain embodiments, the components are combined in a manner to produce a polymer composition wherein at least a portion of the bioactive agent is incorporated within microparticles. Preferably, this results from combining the components in the presence of water (e.g., 5-10 wt-%, based on the total weight of the composition) and then optionally removing a substantial portion of the water (such that less than 1 wt-% water is remaining, based on the total weight of the composition). If desired, all the water can be removed.

In certain embodiments, an inverse emulsion that includes hydrophilic organic microparticles is combined with water and a bioactive agent under conditions effective to distribute (preferably, dissolve) at least a portion of the bioactive agent in the hydrophilic organic microparticles. Optionally, a secondary organic polymer and/or a foaming agent can be added to the mixture of the inverse emulsion, water, and bioactive agent. Once sufficiently mixed to impregnate at least a portion of the bioactive agent (e.g., silver compound) into the hydrophilic particles, the water is removed if desired.

In other embodiments, monomers for a hydrophilic organic polymer are combined with a bioactive agent, and optionally a foaming agent, under conditions effective to polymerize the monomers and distribute (preferably dissolve) at least a portion of the bioactive agent in the hydrophilic organic polymer. The bioactive agent can be present during the polymerization process or added after the polymerization is complete. Optionally, a secondary organic polymer and/or a foaming agent can be added to the hydrophilic organic polymer with the bioactive agent distributed therein.

The polymer compositions with the bioactive agent therein can be melt processed (e.g., extruded or molded) or solvent cast to form the desired products (e.g., wound dressing). If thermally expandable microspheres (or other foaming agents) are present, the composition can be processed under conditions effective to expand the thermally expandable microspheres (or other foaming agents) *in situ* during the extrusion process, or after extrusion of the composition followed by exposure to heat in an oven. Thus, in certain embodiments a method of the present invention includes processing the composition under conditions that do not significantly expand the thermally expandable microspheres and subsequently exposing the extruded material to conditions effective to expand the thermally expandable microspheres.

The materials used to prepare the polymer compositions of the present invention are melt processable if they are fluid or pumpable, and they do not significantly degrade or gel at the temperatures used to melt process (e.g., extruding or compounding) the composition (e.g., at least 50°C and up to 300°C). Preferably, such materials have a melt viscosity of at least 10 poise and often up to 1,000,000 poise, as measured by capillary melt rheometry at the processing temperatures and shear rates employed in extrusion. Typically, suitable materials possess a melt viscosity within

this range at a temperature of at least 175°C and often up to 225°C and a shear rate of 100 seconds^{-1}.

Continuous melt process forming methods include drawing the extruded composition out of a film die and subsequently contacting a moving plastic web or other suitable backing. Another continuous forming method involves directly contacting the extruded composition to a rapidly moving plastic web or other suitable substrate. In this method, the extruded composition can be applied to a moving web using a die having flexible die lips such a reverse orifice coating die and other contact dies using rotating rods. The composition can also be extruded in the form of continuous fibers and blown micro-fiber webs as disclosed in Wente, Van A., "Superfine Thermoplastic Fibers," Industrial Engineering Chemistry, Vol. 48, pp. 1342-1346; Wente, Van A. et al., "Manufacture of Superfine Organic Fibers," Report No. 4364 of the Naval Research Laboratories, published May 25, 1954; U.S. Pat. No. 5,176,952 and U.S. Pat. No. 3,841,953. After melt process forming the composition is solidified by quenching using either direct methods, such as chill rolls or water baths, or indirect methods, such as air or gas impingement, or both.

In some embodiments, a non-adherent or adherent composition (which can be in the form of a gel) is preferably obtained by hot mixing without a solvent (so-called hot-melt process), by blending an elastomer with an oily plasticizer and antioxidants, and then by adding a hydrocolloid either as finely divided powder or as an inverse emulsion. If active agents are provided, these may be added to either the elastomer or the hydrocolloid.

Articles can be prepared using compositions described herein according to a variety of methods, particularly coating methods. When a porous substrate is coated, the process of coating the porous substrate with the composition typically allows the yarns, filaments, or film to be properly trapped in the composition, while leaving most of the apertures unobstructed by the composition. Depending on the structure of the support used, the amount of composition employed will vary over a wide range (typically from 50 grams per square meter (g/m^2) to 300 g/m^2, and preferably from 60 g/m^2 to 160 g/m^2).

In certain embodiments, the coating can be carried out hot, without a solvent, using a continuous process in which the substrate is directed over a first coating roll covered with a layer of molten composition having a predetermined thickness, and then

over a second roll which removes the composition lying within the apertures of the substrate. The substrate thus covered with gel only on the yarns, filaments, or film is then cooled in a stream of air so that the composition cannot flow and remains uniformly distributed around the yarns, filaments, or film. If necessary, a system producing a laminar stream of air is provided, which system is able both to correct the distribution of the composition around the yarns, filaments, or film and to unblock any substrate apertures, which would not have been open in the previous step of the process.

According to a variant of this process, a substrate can be passed through a bath of molten polymeric composition (for example, at a temperature of 120°C to 200°C). The substrate covered with molten composition is then passed between two fixed rolls pressed against each other with a predetermined gap, so as to remove the excess composition. The amount of composition remaining on the yarns, filaments, or film depends essentially on the gap set between the fixed rolls. The covered process is then cooled and treated in a manner similar to the previous process.

If desired, the cooled coated substrate can be covered with two protective films (for example, thin polyester films). These films may or may not require a nonstick treatment and can function to facilitate extraction from a package and in handling the article. If desired, the coated substrate can be cut into individual compresses, of sizes suitable for the use, packaged in sealed sachets, and sterilized.

Solvent casting may also be used to prepare the articles of the present invention. This method typically employs a common solvent, selected for compatibility with the polymer composition components. Such common solvents include, for example, toluene and tetrahydrofuran. Specific selection of a common solvent for a particular subset of the present invention is within the skill of the art. In the solvent casting method, the materials included in the composition are blended to form a uniform mixture, then coated onto a carrier web or a backing (described below) using a known coating technique such as curtain coating, die coating, knife coating, roll coating, or spray coating. A preferred coating method is knife coating. The solvent is then removed from the coated backing, usually with the aid of a drying oven for a time and temperature selected to remove any undesirable level of residual solvent.

Layered constructions can also be prepared using lamination, coating, or extrusion techniques known to one of skill in the art and as described, for example, in U.S. Pat. No. 6,379,791.

If desired, compositions of the present invention can be sterilized. Methods of sterilization include treatment with electron beam or gamma radiation.

MEDICAL ARTICLES

The polymer compositions of the present invention can be used in a wide variety of products, although they are preferably used in medical articles. Such medical articles can be in the form of a wound dressing, wound packing material, or other material that is applied directly to or contacts a wound.

Such articles may or may not include a backing (i.e., a support substrate). If a backing or support substrate is desired, it can be porous or nonporous. The composition of the present invention can be coated on the support substrate or impregnated into it, for example.

Suitable materials are preferably flexible, and may be fabric, non-woven or woven polymeric films, metallic foils, paper, and/or combinations thereof. More specifically, film backings are useful with the polymer compositions of the present invention. For certain embodiments it is desirable to use a permeable (e.g., with respect to moisture vapor), open apertured substrate (i.e., a scrim). For certain embodiments it is desirable to use an open- or closed-cell foam, such as that disclosed in U.S. Patent Nos. 6,548,727 and 5,409,472.

The porous substrates (i.e., backings) are preferably porous to allow the passage of wound fluids, moisture vapor, and air. In certain embodiments, the porous substrates are substantially impervious to liquid, especially wound exudate. In certain embodiments, the porous substrates are capable of absorbing liquid, especially wound exudate. In certain embodiments, the porous substrate is an apertured, liquid permeable substrate.

Suitable porous substrates include knits, wovens (e.g., cheese cloth and gauze), nonwovens (including spun-bonded nonwovens), extruded porous sheets, and perforated sheets. The apertures (i.e., openings) in the porous substrates are of sufficient size and sufficient number to facilitate high breathability. For certain embodiments, the porous substrates have at least 1 aperture per square centimeter. For

certain embodiments, the porous substrates have no greater than 225 apertures per square centimeter. For certain embodiments, the apertures have an average opening size (i.e., the largest dimension of the opening) of at least 0.1 millimeter (mm). For certain embodiments, the apertures have an average opening size (i.e., the largest dimension of the opening) of no greater than 0.5 cm.

For certain embodiments, the porous substrates have a basis weight of at least 5 grams/meter^2. For certain embodiments, the porous substrates have a basis weight of no greater than 200 grams/meter^2.

The porous substrates (i.e., backings) are preferably flexible yet resistant to tearing. For certain embodiments, the thickness of the porous substrates is at least 0.0125 mm. For certain embodiments, the thickness of the porous substrates is no greater than 3 mm.

The porous substrates may be opaque or translucent. Normally they have a skin color, but "designer" colors and patterns, as well as cartoon character designs, are becoming popular.

Materials of the backing or support substrate include a wide variety of materials including paper, natural or synthetic fibers, threads and yarns made from materials such as cotton, rayon, wool, hemp, jute, nylon, polyesters, polyacetates, polyacrylics, alginates, ethylene-propylene-diene rubbers, natural rubber, polyesters, polyisobutylenes, polyolefins (e.g., polypropylene polyethylene, ethylene propylene copolymers, and ethylene butylene copolymers), polyurethanes (including polyurethane foams), vinyls including polyvinylchloride and ethylene-vinyl acetate, polyamides, polystyrenes, fiberglass, ceramic fibers, and/or combinations thereof.

The backing can also be provided with stretch-release properties. Stretch-release refers to the property of an adhesive article characterized in that, when the article is pulled from a surface, the article detaches from the surface without leaving significant visible residue. For example, a film backing can be formed from a highly extensible and highly elastic composition that includes elastomeric and thermoplastic A-B-A block copolymers, having a low rubber modulus, a lengthwise elongation to break of at least 200%, and a 50% rubber modulus of not above 2,000 pounds/square inch (13.8 megapascals (MPa)). Such backings are described in U.S. Pat. No. 4,024,312 (Korpman). Alternatively, the backing can be highly extensible and

substantially non-recoverable such as those described in U.S. Pat. No. 5,516,581 (Kreckel et al,).

Pressure sensitive adhesives used in medical articles can be used in articles of the present invention. That is, a pressure sensitive adhesive material could be applied to the article of this invention, for example, around the periphery, to adhere the article to the skin.

In another aspect, the compositions of the present invention will be in the form of an aqueous gel. Suitable gelling agents include polyoxyethylene-polyoxypropylene diol block copolymers, polyacrylic acid lightly crosslinked with triallyl sucrose which has been neutralised using an alkali metal hydroxide, cellulosic derivatives such as carboxymethyl cellulose, hydroxymethyl cellulose, natural gums, and the like. It will be appreciated that care must be taken to avoid using gelling agents that are incompatible with that bioactive agent, such as silver ions. Suitable gel forming block copolymers of polyoxyethylene- polyoxypropylene will have a molecular weight from 4,600 to 13,500 (approximately) and will be present in the gel in an amount from 50% for the lower molecular weight copolymers to 20% for the higher molecular weight copolymers, so that the gel when applied topically is neither too stiff nor too fluid. Typically the gels are formed by mixing together the copolymer and water to form an aqueous solution at a temperature of 2°C and adding the bioactive agent (e.g., silver compound) and then allowing the solution to gel as it warms to ambient temperature. A preferred group of gelling agents are the polyoxyethylene-polyoxypropylene diol block copolymers which are commercially available under the trade designation PLURONICS from BASF-Wyandotte (e.g., PLURONICS F108, F127, and P105).

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Materials

IRGACURE 2959 – UV photo-initiator, available from Ciba Specialty Chemicals, Tarrytown, New York.

AGEFLEX FAIQ80MC - 2-(dimethylamino)ethylacrylate methyl chloride quaternary salt (80 wt-% in water) available from Ciba Specialty Chemicals, Tarrytown, New York.

KRATON D1107 – styrene-isoprene-styrene thermoplastic elastomer available from Kraton Polymers, Houston, Texas.

KRATON D4433 - a pre-compounded KRATON D1112 and mineral oil (77/23) blend, where the KRATON D1112P is a linear polystyrene-polyisoprene-polystyrene (SIS) thermoplastic elastomeric copolymer having 15 wt-% polystyrene. The blend is available from Kraton Polymers, Houston, Texas.

KRATON D1124K - radial 4-arm star polystyrene-polyisoprene $(SI)_4$ thermoplastic elastomeric copolymer having 30 wt-% polystyrene available from Kraton Polymers, Houston, Texas.

KAYDOL - mineral oil available from Crompton Corporation, formerly Witco Corporation.

ESCOREZ 1310LC – aliphatic C5 tackifying resin compatible with isoprene block of KRATON D1107 available from Exxon Chemical Company.

IRGANOX 1010 – antioxidant available from Ciba Specialty Chemicals, Tarrytown, New York.

SALCARE SC91 – 50 wt-% solids cosmetic grade emulsion having micro-particles of chemically crosslinked hydrophilic anionic sodium acrylates copolymer in mineral and paraffin oils available from Ciba Specialty Chemicals, High Point, North Carolina.

SALCARE SC95 – 50 wt-% solids cosmetic grade emulsion having micro-particles of chemically crosslinked hydrophilic cationic quaternary ammonium acrylate polymer (methylchloride quaternary ammonium salt of DMAEMA) in mineral and paraffin oils available from Ciba Specialty Chemicals, High Point, North Carolina.

SALCARE SC96 - 50 wt-% solids cosmetic grade emulsion having micro-particles of chemically crosslinked hydrophilic cationic quaternary ammonium acrylate polymer (methylchloride quaternary ammonium salt of DMAEMA) in propylene glycol dicaprylate dicaprate available from Ciba Specialty Chemicals, High Point, North Carolina.

DMAEMA – 2-(dimethylamino)ethyl methacrylate polymer.

Silver Nitrate ($AgNO_3$) – 99+% reagent grade; Formula Weight (FW) is 169.88 from Aldrich (Milwaukee, Wisconsin) used to make a 5.6M $AgNO_3$ solution by dissolving the as received $AgNO_3$ in water..

MICROPEARL F100D – thermally expandable micro-sphere physical foaming agent available from Pierce and Stevens,Buffalo, New York.

Trypticase (Tryptic) Soy Broth (TSB) medium available from Becton Dickinson & Company, Bedford, Massachusetts.

Polyester Knitted Fabric was a 24 mesh polyester knit ($61g/m^2$) purchased from Lamports Filter Media, Inc, Cleveland, OH.

Absorbency Tests

Bovine Serum Absorbency Test

A dry wound dressing sample (10 cm x 15 cm) was applied to the upper flange of a clear polycarbonate cup, similar to a Paddington cup as described in the British Pharmacopoeia, 1993, Addendum 1996, page 1943, HMSO London, England. The sample was positioned over the center of the cup cavity (3.8-centimeter (cm) diameter, 3-cm depth, 14-mL volume capacity) and the sample was held in place by its own pressure sensitive adhesive layer. The cup was then inverted and 12 grams (g) of calf bovine serum (Sigma-Aldrich Chemical Co.) was added to the cup through a port. The port was closed with a threaded plug and the cup was placed in an incubator at 40°C and 20% RH. After 24, 48, and 72 hours the amount of unabsorbed serum was removed, weighed (W_t), and then added back into the cup. The cup plus sample were then returned to the incubator until the next sampling timepoint. The absorbency was calculated using the following formula and the results reported in grams as an average of three replications:

Calf Bovine Serum Absorbency (g) = 12 g – W_t

Saline Absorbency Test

Samples (2.54 cm by 2.54 cm) were soaked in saline. The samples were removed from the saline at various times and were lightly dabbed with a paper towel. The weight was recorded and the samples were placed back into the saline solution. The weight of saline absorbed per weight of dry coating was calculated as a function of swelling time in the saline using the following equation: (weight saline absorbed)/(dry

coating sample weight) = [(saline swollen weight) – (dry sample weight)]/[(dry sample weight) – (weight of substrate)].

Anti-microbial Performance Tests

2 Hours % Live Bacteria Test

The effectiveness of a sample was tested using a L-7012, Bacterial Viability Kit, available from Molecular Probes (Eugene, Oregon). The procedure is outlined below using the red, propidium iodide dye, and green, SYTO 9 dye, contained in the kit to stain the live and dead bacteria.

Preparation of bacteria solution: Staphylococcus aureus bacteria were grown in Trypticase (Tryptic) Soy Broth (TSB) medium overnight. Bacteria were concentrated by centrifugation at 10,000 x gravity for 15 minutes (min). Supernatant was removed and the pellet was re-suspended in MilliQ water (filtered through a 0.2 μm pore-size filter) or in Butterfield phosphate buffer (from Hardy Diagnostics, Santa Maria, California). Bacteria solution was diluted to the desired bacteria concentration (10^7 cells/milliliters) by measuring the optical density (OD) at 670 nm. For a control experiment, the bacteria solution was incubated with 70% isopropyl alcohol at room temperature for 1 hour (hr) to measure the killed bacteria control. Different volume of live and dead bacteria solutions were mixed to generate a range of percent live solution for calibration purposes.

Sample preparation: All prototypes were prepared by punching out a 1-inch (2.54-cm) diameter samples using a stainless steel punch; sometimes as indicated in the examples a 1-inch (2.54 cm) disk was further cut with scissors in eighths and then evaluated. The amount of sample was weighed, and then transferred to 50 milliliters (mL) sterile conical tubes.

Bacteria labeling and Anti-microbial testing: 7 mL of bacteria solution at initial concentration of approximately $1x10^8$ bacteria/mL were pipetted into a 50 mL conical tube containing the sample. At the specified time (e.g., 2 hours (hr)), 50 microliter (μL) of the supernatant was pipetted into fluorescent measurement tube which already contained 450 μL of MiliQ water and premixed green dye and red dye solution (1.5 μL dye mixture for 500 μL bacteria solution) was added and the mixture was incubated for 15 minutes in the dark at room temperature. These solutions were then measured by flow cytometry. Cell viability was measured using the BD FACSCaliber flow

cytometer (made by Becton Dickinson & Company, Franklin Lakes, New Jersey). The flow cytometer is equipped with an argon-ion laser at 488 nanometers (nm) and 15 milliWatts (mW) output. Data acquisition and analysis were controlled using CellQuest software and PBPAC hardware interface. The light path contained a 488/10 nm blocking filter, then a 530/30 nm filter before the green PMT and a 585/42 nm long pass filter before the red PMT. The sampling rate was around 3000-7000 particles/second. The sheath fluid was FACSFlow by Becton Dickinson. The instrument voltage was 5.5 Volt.

The live cell and dead bacteria responses were established with the 100 % live cell and 100% dead cell (for killed bacteria, bacteria solution was incubated with 70% isopropyl alcohol at room temperature for 1 hr) samples. Different volumes of live and dead bacteria solutions were mixed to generate a range of percent live solutions for calibration purposes. The sample results for bacteria killing ability were interpolated from the standard curve generated from calibration samples. Total bacteria concentration was determined by the measuring of the OD at 670 nm of the bacteria solution.

Zone of Inhibition Test

Anti-microbial performance was measured using a Zone of Inhibition test (ZOI) that was performed by the following method. Mueller-Hinton agar was prepared, sterilized and tempered in a water bath at 48-50°C. A suspension of bacteria in sterile phosphate-buffered water was prepared with approximately 10^8 CFU/ml. The agar was cooled to 48-50°C, inoculated with the bacterial suspension to an approximate concentration of 10^5 CFU/ml (1:1000). The inoculated agar was swirled to mix and pipetted (approximately 14 ml) into sterile Petri dishes (15 x 100 mm). The seeded agar was allowed to set for about 20 minutes to harden. An alcohol-disinfected die and cutting board were used to cut textile samples to desired size. Sterile forceps were used to place the samples onto the seeded, hardened agar in center of plate. The plate was then placed into an incubator at 35-37°C for overnight (16-24 hours) incubation. After incubation the clear zones, no visible colonies formed, were measured in millimeters (mm) with calipers.

The zone of inhibition (ZOI) is then calculated by the following equation:

ZOI = [diameter of clear zone (mm) – diameter of sample (mm)]/2.

Peel Adhesion Test

Peel adhesion is measured as 180° peel from steel plates, at 23°C, 50% relative humidity (RH), 305 millimeters per minute (mm/min), 25mm wide using a Model 3M90 Slip/Peel tester (IMASS, Inc., Accord, MA). The samples were conditioned for 24 hours at controlled temperature and humidity. After conditioning the samples were adhered to a stainless steel panel using 2 kilogram (kg) roller and 4 passes. The samples were peeled from the stainless steel plate after 15 minutes of dwell time using a 0.305 meter/minute (m/min) peel rate. Typically two 0.13 meter (m) long samples were measured and the average peel force recorded in ounces/inch (oz/in) and converted to Newtons per decimeter (N/dm).

Example 1

A solution of 18.2 grams (g) 2-(dimethylamino)ethylacrylate methyl chloride quaternary salt (80% in water; AGEFLEX FAIQ80MC), 0.04 g of IRGACURE 2959, 1.61 g of 2M (2 molar) NaCl aqueous solution and 0.12 g polyethylene glycol 600 diacrylate were added to a glass vial and mixed well. To this mixture was added 0.72 g of 1M $AgNO_3$ aqueous solution and the glass vial was capped. The vial was heated and shaken in a hot water bath until a clear solution was obtained. The solution was placed between clear silicone coated release liners and irradiated with UV light (approximately 3000 millijoules per square centimeter (mJ/cm^2)) to produce a clear polymer. Non-stable compositions darkened (black or yellow) during UV irradiation. A 1-inch (25.4-millimeter (mm)) diameter disk of this material was gamma irradiated and then tested for anti-microbial activity against Staphylococcus aureus bacteria using the 2 Hours % Live Bacteria Test. Test results indicated 73% of the bacteria were alive after 2 hours.

Example 2

A solution of 17.5 g of 2-(dimethylamino)ethylacrylate methyl chloride quaternary salt (80% in water) and 0.04 g of IRGACURE 2959 were mixed together. While this mixture was stirring, 2.5 g of a 1M $AgNO_3$ aqueous solution was added in small aliquots. The glass vial was capped. The vial was heated and shaken in a hot water bath until a clear solution was obtained. The solution was poured into a mould and cured between silicone release liners for 12 minutes under UV lights. The 40 mils

(1 mm) thick silver polymer matrix was gamma irradiated and tested for anti-microbial activity against *Staphylococcus aureus* bacteria using the 2 Hours % Live Bacteria Test. A 1-inch (25.4-mm) diameter circle killed all the bacteria within 2 hours. Further, one eighth of a 1-inch (25.4 mm) diameter (0.036 g) circle killed all the bacteria within 2 hours.

Example 3

A solution of 17.5 g of 2-(dimethylamino)ethylacrylate methyl chloride quaternary salt (80% in water) and 0.04 g of IRGACURE 2959 were mixed together. While this mixture was stirring, 2.5 g of a 1M $AgNO_3$ aqueous solution was added in small aliquots, and 1.18 g of deionized (DI) water was then added. The glass vial was heated and shaken in a hot water bath until a clear solution was obtained. The solution was placed between silicone coated release liners and irradiated with UV light (approximately 3000 mJ/cm^2) to produce a clear polymer. The silver polymer matrix was clear after polymerization. Adding more water made the silver/monomer solution become cloudy.

Example 4

A solution of 14.5 g of 2-(dimethylamino)ethylacrylate methyl chloride quaternary salt (80% in water) and 0.04 g of IRGACURE 2959 were mixed together in a glass vial. While this mixture was stirring, 2.5 g of a 1M $AgNO_3$ aqueous solution was added in small aliquots. Three grams (3 g) of 2-hydroxyethylmethacrylate was then added and the glass vial was capped. The vial was heated and shaken under hot water until a clear solution was obtained. The solution was placed between silicone coated release liners and irradiated with UV light (approximately 3000 mJ/cm^2) to produce a clear polymer. The 40 mils (1 mm) thick clear silver polymer matrix was gamma irradiated and tested for anti-microbial activity against *Staphylococcus aureus* bacteria using the 2 Hours % Live Bacteria Test. A 1-inch (25.4 mm) diameter (0.036 g) circle killed 48 % of the bacteria within 2 hours.

Example 5

A solution of 11.5 g of 2-(dimethylamino)ethylacrylate methyl chloride quaternary salt (80% in water) and 0.04 gram of IRGACURE 2959 were mixed

together. While this mixture was stirring, 2.5 g of a 1M $AgNO_3$ aqueous solution was added in small aliquots. Six grams of 2-hydroxyethylmethacrylate was then added and the solution turned white. The solution was then placed between silicone coated release liners and irradiated with UV light (approximately 3000 mJ/cm^2) to produce a black colored polymer. Even though this example falls within the scope of the invention it would not preferred for most uses due to the black color that develops on UV irradiation.

Example 6

An absorbent foamed film that was used to make Example 6 was prepared by gravimetrically feeding KRATON D1107P thermoplastic elastomer pellets at 53 grams per minute feed rate into the feed throat (barrel 1) of a 30 millimeter (mm) diameter, fully intermeshing and co-rotating twin-screw extruder (Werner Pfleiderer ZSK30) having nine barrels and a length to diameter ratio of 27 to 1. A mixture of ESCOREZ 1310LC solid tackifying resin and IRGANOX 1010 anti-oxidant was melted at 350°F (177°C) and injected into barrel 2 at 53 grams per minute feed rate using a Dynisco grid-melter with a discharging Zenith gear pump. SALCARE SC95 inverse-emulsion polymer was injected at room temperature (22°C) and 75.6 grams per minute feed rate into barrel 4 using a Zenith gear pump. MICROPEARL F100D foaming agent was gravimetrically fed into barrel 7 at 4.5 grams per minute flow rate using an auxiliary single-screw conveying device. The temperatures of the twin-screw extruder (TSE) were maintained at full cooling, 300°F (149°C), 400°F (204°C), 300°F (149°C), 240°F (116°C), 225°F (107°C), 225°F (107°C), 250°F (121°C) and 300°F (149°C) for barrel 1 through 9, respectively. The TSE was controlled at 200 revolutions per minute (rpm). The TSE was discharged using a Zenith gear pump into a 6-inch (15.24-centimeter (cm)) wide single-orifice film die using a conveying hose. The hose, pump and die were all maintained at 300°F (149°C). The film die gap was set to 0.040 inch (1.0 mm). The TSE temperature profile was controlled so that the foaming agent would not start expanding until the end of the TSE. Continued expansion was facilitated in both the conveying hose and film die. The foamed composition was extruded onto 2 paper release liners that were contacted to two polished and chromed steel rolls that were maintained at 40°F (4°C) and 0.040 inch (1.0 mm) gap. The chilled rolls were set at 3 feet (0.9 meter) per minute take-away speed to provide a 0.040 inch (1.0 mm) thick

foamed film having 0.5 gram per cubic centimeter (g/cc) density at 22°C. The composition of the resulting foam was 34 wt-% KRATON D1107, 33 wt-% ESCOREZ 1310LC, 1 wt-% IRGANOX 1010, 29 wt-% SALCARE SC95 and 3 wt-% MICROPEARL F100D.

Example 6 was prepared by soaking this extruded foam in a 0.01N (Normal) silver nitrate solution for 6 hours. The soaked foam was subsequently dried for 24 hours at 175°F (79°C). The silver nitrate containing foam (Example 6) was analyzed for the timed release of silver ion upon re-hydration with saline solution using inductively coupled plasma-mass spectrometry (ICPMS). A 2 cm diameter disc of Example 6 was placed into 20 mL of a 0.8 wt-% saline solution at 38°C (approximately human body temperature). After 24 hours the swelled foam was removed from the solution. One milliliter (1 mL) of the remaining solution was diluted to 10 mL with saline. The swelled disc of Example 6 was then placed in a fresh 20 mL of saline and soaked for another 24 hours. Once again, the disc was removed and the process repeated for one more soaking. In a separate measurement, a fresh disc of Example 6 was placed in 20 mL of fresh saline and the sample was removed after 72 hours. The amount of silver ion that was leached out of the Example 6 foam as it was re-hydrated in the saline solution for each of the four leachates was measured using a Perkin Elmer Elan 6000 ICPMS against silver standard dissolved in a 5 wt-% nitric acid solution. Due to interference by the presence of sodium chloride the amounts of silver ion are lower estimates. Table 2 summarizes the ICPMS silver ion concentration analysis of the silver nitrate containing foam leachates for Example 6.

Table 2

[Ag+] after 1st 24 hour saline soak (µg/20 mL)	[Ag+] after 2nd 24 hour saline soak (µg/20 mL)	[Ag+] after 3rd 24 hour saline soak (µg/20 mL)	Cumulative [Ag+] after 3 – 24 hour saline soaks (µg/20 mL)	[Ag+] after single 72 hour saline soak (µg/20 mL)
> 9.5	> 9.5	> 9.5	> 28.5	> 9.7

This analysis demonstrates that silver ions are continually leached out of Example 6 after 72 hours of re-hydration in saline solution.

Examples 7-8

The foamed film described in Example 6 was impregnated with two concentrations of silver nitrate solutions. Examples 7 and 8 were prepared by using a #30 Meyer bar to coat a 0.003 inch (0.08 mm) thick coating of either 0.01N (Example 7) or 0.1N silver nitrate solution (Example 8) onto the surface of the foam. The coated foams were dried at 150°C for 15 minutes. Example 8 absorbed 185 weight percent (wt-%) saline solution after 24 hours of swelling time.

Example 7 (0.01N silver nitrate coating) and Example 8 (0.1N silver nitrate coating) were analyzed for anti-microbial performance using the 2 Hours % Live Bacteria Test with the modifications as listed. The initial live bacteria concentration was approximately 1 x 10^8 counts per mL of deionized water. A 2 cm diameter disc of the example was placed in a 5 mL solution of the live bacteria. After 2 hours of contact the percentage of live bacteria left in the solution was measured. Both Examples 7 and 8 provided for 100% kill of all live bacterial counts.

Comparative Example 9 and Examples 10-11

Comparative Example 9 and Examples 10-11 were prepared in the same manner as Example 6 with the following modifications. KRATON D1107 was gravimetrically fed at 35 grams per minute flow rate into the feed throat (barrel 1) of the TSE. A mixture of ESCOREZ 1310LC and IRGANOX 1010 (IRG. 1010) was melted at 350°F (177°C) and injected at 35 grams per minute flow rate into barrel 4. SALCARE SC95 was injected at room temperature at 76 grams per minute flow rate into barrel 5. The foaming agent (MICROPEARL F100D) was gravimetrically fed in the same manner as for Example 6 at 4.5 grams per minute into barrel 7. A 0.1N silver nitrate solution was dripped into barrel 7 using a peristaltic pump at either 10 grams per minute (Example 10) or 19.2 grams per minute (Example 11). For Comparative Example 9, 19.2 grams per minute of deionized water was dripped into barrel 7 instead of the silver nitrate solution.

The temperatures of the twin-screw extruder (TSE) were maintained at full cooling, 250°F (121°C), 375°F (191°C), 300°F (149°C), 255°F (124°C), 215°F (102°C), 215°F (102°C), 180°F (82°C) and 265°F (129°C) for barrel 1 through 9, respectively. The TSE was controlled at 400 revolutions per minute (rpm). The film

die gap was set to 0.060 inch (1.5 mm). The foamed compositions were extruded onto 2 paper release liners that were contacted to two polished and chromed steel rolls that were maintained at 40°F (4°C) and 0.060 inch (1.5 mm) gap. The chilled rolls were set at 3 feet (0.9 meter) per minute take-away speed to provide 0.060-inch (1.5-mm) thick foamed films.

Comparative Example 9 and Examples 10-11 were laminated to 3M TEGADERM adhesive film and sterilized using gamma irradiation at 24.7 kilograys (kGy) dosage. The samples were tested for absorption of bovine serum albumin (BSA) using the Bovine Serum Albumen Absorbency Test. Examples 10 and 11 were tested using the modified 2 Hours % Live Bacteria Test in the same manner as described for Examples 7 and 8. Table 3 contains the compositional information and Table 4 contains the BSA absorbency and the 2 hours % live bacteria test results for Comparative Example 9 and Examples 10-11.

Table 3

Ex	KRATON D1107 (wt-%)	ESCOREZ 1310LC (wt-%)	SALCARE SC95 (wt-%)	MICRO-PEARL F100D (wt-%)	IRG. 1010 (wt-%)	DI Water (wt-%)	$AgNO_3$ (wt-%)
9 (Comp)	20.62	20.21	44.78	2.65	0.41	11.31	0
10	21.81	21.37	47.35	2.80	0.44	6.12	0.11
11	20.62	20.21	44.78	2.65	0.41	11.12	0.19

Table 4

Ex	Density (g/cc)	$AgNO_3$ (wt-%)	Initial Weight (grams)	24 Hr. BSA Absorb. (wt-%)	48 Hr. BSA Absorb. (wt-%)	72 Hr. BSA Absorb. (wt-%)	2 Hours % Live Bacteria
9 (Comp)	0.56	0	0.57	647	937	1172	55.1
10	0.72	0.11	0.65	582	865	1092	32.9
11	0.73	0.19	0.75	483	684	859	6.4

Comparative Examples 12,16-18 and Examples 13-15

Fifty (50) grams of deionized (DI) water and 50 grams of silver nitrate (formula weight 169.87) were dissolved to make a 5.89 molar silver nitrate solution. One hundred (100) grams of either SALCARE SC95, SC96, or SC91 were placed in a WARING blender 7012 Model 34BL21 and stirred at the lowest motor setting. Either 1 or 2 milliliters of a 5.89M silver nitrate solution were added drop-wise with a 22 gauge, 1.5-inch (3.75 cm) long stainless steel syringe needle at a rate of 1 drop per second. Once all of the silver nitrate solution had been added, 1 drop of the silver/SALCARE dispersion was placed between two microscope slides and subsequently exposed to 30 minutes of sunlight. Table 5 summarizes the compositions and sunlight stability of Comparative Examples 12,16-18 and Examples 13-15.

Table 5

Ex	SALCARE SC91 (wt-%)	SALCARE SC95 (wt-%)	SALCARE SC96 (wt-%)	$AgNO_3$ (wt-%)	Did the example darken with sunlight exposure?
12 (Comp)	0	0	100	0	No
13	0	0	99	1	No
14	0	0	98	2	No
15	0	98	0	2	No
16 (Comp)	100	0	0	0	No
17 (Comp)	99	0	0	1	Yes
18 (Comp)	98	0	0	2	Yes

The sunlight exposure results presented in Table 5 demonstrate that both the SALCARE SC96 and SC95 mixtures with silver nitrate provided for light stability whereas the presence of SALCARE SC91 did not.

Some of the Examples were tested for anti-microbial activity against *Staph. aureas* using the 2 Hour % Live Bacteria Test. Two drops of the silver/SALCARE dispersion was dripped into the bacterial solution. All bacterial solution volumes were 7 milliliters (mL). The results are tabulated in Table 6. These results can be compared to a standard solution of 0.5 wt-% silver nitrate in DI (containing a calculated Ag^+ weight of 22,224 μg), which demonstrated 15.8% live bacteria after 2 hours.

Table 6

Example	Sample Weight (grams)	Calc. Silver Salt Weight (μg)	Calc. Ag^+ Weight (μg)	Initial Live Bacteria Concentration (bacteria/mL)	% Live after 2 hours
13	0.040	400	254	1.8×10^8	8.2
14	0.040	800	508	1.8×10^8	9.3
15	0.040	800	508	1.8×10^8	38.8

Examples 19-21 and Comparative Example 22

Examples 19-21 were prepared in the same manner as Comparative Example 9 and Examples 10-11 except for the following modifications. Two mixtures of SALCARE SC95 emulsion and silver nitrate solutions were prepared by blending a 50 wt-% silver nitrate in deionized water solution into the emulsion using a double planetary Ross mixer. The resulting mixtures consisted of either 98/1/1 or 96/2/2 SALCARE SC95/silver nitrate/deionized water, all in weight percentages. KRATON D1107 was gravimetrically fed into the feed throat (barrel 1) of the TSE. A 98/2 mixture of ESCOREZ 1310LC and IRGANOX 1010 was melted at 350°F (177°C) and injected into barrel 4. The SALCARE SC95/silver nitrate/deionized water mixture was injected at room temperature into barrel 5. The foaming agent (MICROPEARL F100D) was gravimetrically fed in the same manner as for Example 6 into barrel 7 for Examples 10-11.

The temperatures of the twin-screw extruder (TSE) were maintained at full cooling, 300°F (149°C), 400°F (204°C), 300°F (149°C), 240°F (116°C), 225°F (107°C), 225°F (107°C), 250°F (121°C) and 300°F (149°C) for barrel 1 through 9, respectively. The TSE was controlled at 200 revolutions per minute (rpm). The total material throughputs were 151.33 grams per minute and 155.87 grams per minute for Example 19 and Examples 20-21, respectively. The film die gap was set to 0.015 inch (0.25 mm) for Example 19 and 0.060 inch (1.0 mm) for Examples 20-21.

The compositions were extruded onto 2 paper release liners that were contacted to two polished and chromed steel rolls that were maintained at 40°F (4°C) at 0.015 inch (0.25 mm) gap for Example 19 and 0.060 inch (1.5 mm) gap for Examples 20-21. The chilled rolls were set at 3 feet (0.9 meter) per minute take-away speed to provide 0.015-inch (0.25-mm) or 0.060-inch (1.5-mm) thick films for Example 19 and Examples 20-21, respectively. The un-foamed Example 19 had an approximate density of 1.0 gram/cm^3 whereas the foamed Examples 20-21 had an approximate density of 0.6 gram/cm^3. Table 7 contains the compositional information and for Examples 19-21.

Table 7

Ex	KRATON D1107 (wt-%)	ESCOREZ 1310LC (wt-%)	SALCARE SC95 (wt-%)	MICRO-PEARL F100D (wt-%)	IRG. 1010 (wt-%)	DI Water (wt-%)	$AgNO_3$ (wt-%)
19	25.00	24.00	49.00	0.00	1.00	0.50	0.50
20	24.27	23.30	47.58	2.91	0.97	0.49	0.49
21	24.27	23.30	46.61	2.91	0.97	0.97	0.97

Examples 19-21 and Comparative Example 22 (Contreet H silver hydrocolloid dressing, available from Coloplast Pty. Limited) were evaluated for anti-microbial activity against Staph. aureas using the 2 Hour % Live Bacteria test. All solution volumes were 7 mL. The results are summarized in Table 8.

Table 8

Example	Sample Weight (grams)	Calc. $AgNO_3$ Weight (μg)	Calc. Ag+ Weight (μg)	Initial Live Bacteria Concentration (bacteria/mL)	% Live after 2 hours
19	0.1247	624	396	1.8×10^8	53.1
20	0.0787	394	250	1.8×10^8	30.4
21	0.0718	718	456	1.8×10^8	28.8
22 (Comp)	0.120	Unknown	Unknown	1.8×10^8	95.5

Examples 23-24

Examples 23 and 24 were prepared by first preparing a gel as described below and combining that with a lot of silver modified Salcare that was prepared as outlined below.

Preparation of Gel

Two lots of Styrene-isoprene-styrene (SIS) gel were prepared in the following manner. SIS pellets were gravimetrically fed into the feed throat (barrel 1) of a Werner Pfleiderer ZSK30 co-rotating twin-screw extruder (TSE) having a 30 mm diameter barrel and 15 barrel sections. Each temperature zone was a combination of two barrel sections (e.g., Zone 1 corresponded to barrel sections 2 and 3). Barrel section 1 was controlled at full cooling capacity for all SIS gel lots. A powdered antioxidant (IRGANOX 1010) was also gravimetrically fed into barrel section 1 for SIS gel lot 2. KAYDOL mineral oil was heated and added to the TSE as described in International Publication No. WO 97/00163. The disclosed compounding process provides a method for making a gel by melting of the SIS elastomer followed by addition of the heated mineral oil. Heated mineral oil was sequentially injected into barrel sections 4, 6, 8, 10 and 12, respectively. The TSE screw speed for lots 1-2 was controlled to 400 rpm. The TSE temperature profile for lot 1 was controlled to 204°C, 204°C, 204°C, 191°C, 177°C, 149°C, and 149°C for zones 1-7, respectively. The heated oil injections for lot 1 were controlled to 204°C, 204°C, 177°C, 149°C, and 149°C, respectively. The TSE temperature profile for lot 2 was controlled to 204°C, 227°C, 227°C, 204°C, 182°C,

171°C, and 93°C for zones 1-7, respectively. The heated oil injections for lot 2 were controlled to 204°C, 204°C, 204°C, 177°C, and 177°C, respectively. Table 9 contains the material flow rates and Table 10 contains the compositional information for SIS gel lots 1-2.

Table 9. SIS Gel Lot Flow Rates

SIS Gel Lot Number	SIS (g/min)	Barrel Section(S) and Oil addition number and Rate (g/min)					Total KAYDOL Oil (g/min)	IRGANOX 1010 (g/min)	Total Flow Rate (g/min)
		S4 Oil 1	S6 Oil 2	S8 Oil 3	S10 Oil 4	S12 Oil 5			
1	125	41	55	40	30	30	196	-	321
2	227	74	100	120	120	108	522	8	757

Table 10. SIS Gel Lots 1-2 Compositions

SIS Gel Lot Number	SIS Type	SIS (wt-%)	KAYDOL oil (wt-%)	IRGANOX 1010 (wt-%)	Total SIS Elastomer (wt-%)
1	linear	39.0	61.0	-	30.0
2	radial	30.0	69.0	1.0	30.0

Preparation of the Silver-modified Particles

Two lots of silver nitrate-modified SALCARE SC95 were prepared. Lot 1 was prepared by mixing 100 grams of SC95 with 2 milliliters (mls) of 5.6 molar (M) silver nitrate at a high speed using a 2-inch (5.08-cm) diameter, three-blade stainless steel paddle mixer. The silver nitrate solution was added drop wise such that all of the solution was added over ten minutes. After all of the silver nitrate solution was added the mixture was further mixed for another ten minutes. Lot 2 was prepared in a similar manner as Lot 1 except twice as much silver nitrate solution was added and the final mixture was dehydrated in a Ross mixer operating at 60°C, 11 hertz and 28 inches (711

mm) of mercury vacuum for 6 hours. Table 11 contains the compositional information for SALCARE SC95/$AgNO_3$ lots 1-2.

Table 11. SALCARE SC95/$AgNO_3$ Lots 1-2 Compositions

SALCARE SC95 Lot Number	SALCARE SC95 (grams)	SALCARE SC95 (wt-%)	5.6M $AgNO_3$ (ml)	5.6M $AgNO_3$ (wt-%)	DI H_2O (wt-%)
1	100.0	96.0	2.0	2.0	2.0
2	100.0	96.2	4.0	3.8	Dehydrated

Preparation of Examples 23-24

Examples 23-24 were prepared by combining pre-compounded SIS gel lots 1-2 with pre-compounded SALCARE SC95/$AgNO_3$ lots 1-2 in a Haake 25-mm diameter, fully intermeshing counter-rotating TSE. Example 23 was prepared by re-melting SIS gel lot 1 in a Bonnot extruder operating at 127°C. The molten gel was injected at 22.8 grams per minute into barrel section 1 of the TSE. SALCARE SC95 lot 1 was injected at ambient temperature into barrel section 3 at 15.2 grams per minute using a Zenith gear pump. The TSE was controlled at 300 rpm screw speed and 149°C temperature. The total material throughput was 38.0 grams per minute for all Examples. The SIS gel/SALCARE blend was discharged out of the TSE into a transport hose using a Zenith gear pump. The transport hose conveyed the molten gel blend to a 0.15meter (m) wide single orifice film die. The transport hose and die were controlled to 157°C and 159°C, respectively. The molten gel blend was extruded into a nip formed by two polished steel rolls gapped at 0.25 mm and controlled to 106°C. A polyester (PET) knitted fabric (Lamports Filter Media, Inc, Cleveland, OH) having 0.8 mm by 0.7 mm (0.56 mm^2) rectangular open apertures, 0.20 mm thickness and 0.15 meter (m) width was fed into the nip at 1.4 meters per minute (m/min) speed. As the fabric exited the molten gel blend/nip the article was cooled in air before being wound up with an inserted paper release liner. Upon cooling, a coated fabric having 78 grams/m^2 coating weight and 0.75 mm by 0.6 mm (0.45 mm^2) rectangular open apertures was obtained. Example 24 was prepared in the same manner only using Gel lot 2 and SALCARE Lot 2. Table 12 contains the process conditions and Table 13 contains the compositional information for Examples 23-24.

Table 12. Example 23-24 Process Conditions

Ex.	SIS Gel Input (Barrel Section)	SALCARE Input (Barrel Section)	TSE Temp. (°C)	Transport Hose/Die Temp. (°C)	Steel Roll Temp. (°C)	Steel Roll Gap (mm)	Coating Speed (m/min)	Coating Weight (g/m^2)
23	1	3	149	157/159	106	0.25	1.4	78
24	2	4	127	127	110	0.38	2.0	83

Table 13. Example 23-24 compositions

Ex.	SIS gel Type (Lot Number)	SIS (wt-%)	IRGANOX 1010 (wt-%)	SALCARE SC95 Lot #	SALCARE (wt-%)	KAYDOL oil (wt-%)	$AgNO_3$ (wt-%)	DI H_2O (wt-%)
23	Linear (1)	18.0	-	1	38.4	42.0	0.8	0.8
24	Radial (2)	18.0	0.6	2	38.4	41.4	1.6	-

Testing of Example 24 Adhesion

Example 24 (the gel coated PET fabric) and slabs (1 mm thick) having the composition of Example 24 were tested for 180° peel adhesion from stainless steel using the peel adhesion test. Measurements of the instantaneous peel force was measured for two 0.13 m long samples and averaged. The 180° peel adhesion from stainless steel was 0.0 N/dm for both the slab and gel coated PET fabric of Example 24. The extremely low 180° peel adhesion demonstrate the inability of the composition and articles of the invention to form a strong adhesive bond. These low values, for the composition and article, are considered to be non-adhesive or non-adherent.

Testing of Examples 23-24 Absorbency

Examples 23-24 were tested for their ability to absorb 0.8 wt-% NaCl (saline) as outlined in the Saline Absorbency Test. Table 14 contains the amount of saline absorbed as a function of time.

Table 14. Saline Absorbency vs. Time for Examples 23-24

Ex.	SIS gel Type (Lot Number)	SIS (wt-%)	SALCARE Type (Lot Number)	0.5 hour Saline Absorb.	1 hour Saline Absorb.	2 hours Saline Absorb.	6 hours Saline Absorb.	24 hours Saline Absorb.
23	Linear (1)	18.0	SC95 (1)	0.9	1.2	1.3	2.0	2.2
24	Radial (2)	18.0	SC95 (2)	4.5	4.5	4.3	nm	nm

The saline absorbency data demonstrates that the composition and article of the invention can absorb an amount of saline that is 1-5 times their dry weight. All samples remained intact after saline exposure, demonstrating the coatings will remain cohesively intact when swollen in a wound bed environment.

Optical micrographs of Example 24 before and after 2 hours of saline exposure were obtained at 2.5x magnification in reflection mode and analyzed for the size of the aperature by measurements of the resulting micrographs. The aperature area was 0.45 mm^2 as coated and 0.35 mm^2 in the equilibrium saline hydrated state for Example 24. This demonstrates that Example 24 samples still maintain sufficient open area to allow for excess wound fluids to escape the wound bed and yet are substantially absorbent.

Testing of Examples-Anti-microbial performance

Example 24 was tested for anti-microbial performance against *Staph. Aureus* using the Zone of Inhibition Test.

Example 24 was sterilized using a cobalt-γ source at both 25 and 40 kilograys (kGy). The samples were tested in the dry state. All samples had a diameter of 24 mm. Table 15 contains the results from the Zone of Inhibition Test for Example 24 at two sterilization exposure levels and a commercially available silver dressing, Example 25 (Comparative-ACTICOAT available from Smith and Nephew, Largo, Florida).

Table 15. Zone of Inhibition Test Results for Example 24

Ex.	SIS (wt-%)	SALCARE Type (wt-%)	KAYDOL oil (wt-%)	$AgNO_3$ (wt-%)	IRGANOX 1010	20 kGy ZOI (mm)	40 kGy ZOI (mm)	Ave. ZOI (mm)
24	18.0	SC95 (38.4)	41.4	1.6	0.6	3.5	3.7	3.6
25	-	-	-	-		-	-	3.3

The results in Table 15 demonstrate the anti-microbial efficacy of this invention. The silver containing dressings of Example 24 has higher measured ZOI than the Example 25, the commercially available dressing. The relative amount of total silver in a one square inch portion of dressing is 0.9 milligrams (mg) of $AgNO_3$ (0.6 mg Ag^+) in Example 24, calculated from the known material input amounts and coating weight, and 2.9 mg total silver (1.3 mg ammonia soluble silver – the "active" form) for the Example 25 (Wounds 10(6),179-188, 1988 Health Management Publications). Example 24 dressing has significantly less silver, either total or active form and stills performs better in the ZOI test than the comparative sample

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A polymer composition preparable by a method comprising combining components comprising:

an organic polymer matrix;

an inverse emulsion comprising absorbent hydrophilic microparticles, wherein the microparticles when in a substantially nonhydrated form have an average particle size of 10 microns or less, and wherein the microparticles comprise an amine-containing organic polymer selected from the group consisting of a poly(quaternary amine), a polylactam, a polyamide, and combinations thereof;

a bioactive agent selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water; and

an optional foaming agent;

wherein the components are combined in a manner to produce a polymer composition wherein at least a portion of the bioactive agent is incorporated within the microparticles.

2. The polymer composition of claim 1 wherein the microparticles have an average particle size of 1 micron or less when in a substantially nonhydrated form.

3. The polymer composition of claim 2 wherein the microparticles have an average particle size of 0.5 micron or more when in a substantially nonhydrated form.

4. The polymer composition of claim 1 further comprising secondary absorbent particles having an average particle size of greater than 10 microns when in a substantially nonhydrated form.

5. The polymer composition of claim 4 wherein the secondary absorbent particles having an average particle size of greater than 10 microns are superabsorbent.

6. The polymer composition of claim 1 wherein the microparticles are superabsorbent.

7. The polymer composition of claim 1 wherein the organic polymer matrix comprises an elastomeric polymer.

8. The polymer composition of claim 7 wherein the elastomeric polymer is selected from the group consisting of a polyisoprene, a styrene-diene block copolymer, a natural rubber, a polyurethane, a polyether-block-amide, a poly-alpha-olefin, a (C1-C20)acrylic ester of meth(acrylic) acid, an ethylene-octene copolymer, and combinations thereof.

9. The polymer composition of claim 1 wherein the organic polymer matrix comprises a thermoplastic polymer.

10. The polymer composition of claim 9 wherein the thermoplastic polymer is a polyolefin.

11. The polymer composition of claim 1 wherein the organic polymer matrix comprises a hydrophilic polymer.

12. The polymer composition of claim 11 wherein the hydrophilic polymer is selected from the group consisting of a polysaccharide, a polyether, a polyurethane, a polyacrylate, a polyester, and combinations thereof.

13. The polymer composition of claim 1 wherein the amine-containing organic polymer microparticles comprises a quaternary ammonium salt of an organic polymer.

14. The polymer composition of claim 13 wherein the microparticles comprise a cationic homopolymer of the methyl chloride quaternary salt of 2-(dimethylamino)ethyl methacrylate.

15. The polymer composition of claim 1 further comprising an additive selected from the group consisting of a plasticizer, a tackifier, a crosslinking agent, a stabilizer,

an extruding aid, a filler, a pigment, a dye, a swelling agent, a foaming agent, a chain transfer agent, and combinations thereof.

16. The polymer composition of claim 15 wherein the additive is a filler comprising fibers.

17. The polymer composition of claim 1 wherein the organic polymer matrix comprises a mixture of two or more polymers.

18. The polymer composition of claim 1 wherein the microparticles are present in an amount of 1 wt-% to 60 wt-%, based on the total weight of the polymer composition.

19. The polymer composition of claim 1 wherein the composition includes water in an amount of 5 wt-% to 10 wt-%, based on the total weight of the polymer composition.

20. The polymer composition of claim 1 in the form of an extruded film.

21. The polymer composition of claim 1 in the form of a foam.

22. The polymer composition of claim 1 further comprising a foaming agent.

23. The polymer composition of claim 22 wherein the foaming agent is a physical foaming agent.

24. The polymer composition of claim 23 wherein the physical foaming agent comprises thermally expandable microspheres.

25. The polymer composition of claim 24 wherein the composition is stable.

26. The polymer composition of claim 1 wherein the method further comprises combining the components in the presence of water and removing a substantial portion of the water.

27. A polymer composition comprising a hydrophilic amine-containing polymer having a weight average molecular weight of at least 1000 selected from the group consisting of a poly(quaternary amine), a polylactam, a polyamide, and combinations thereof, and a bioactive agent distributed therein, wherein the bioactive agent is selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water.

28. The polymer composition of claim 27 wherein the bioactive agent has a solubility in water of at least 0.1 gram per liter in water.

29. The polymer composition of claim 28 wherein the bioactive agent is a silver salt.

30. The polymer composition of claim 27 wherein the amine-containing polymer is in the form of particles.

31. The polymer composition of claim 30 wherein the particles when in a substantially nonhydrated form have an average particle size of 10 microns or less.

32. The polymer composition of claim 30 wherein the particles are superabsorbent.

33. The polymer composition of claim 27 wherein the amine-containing polymer comprises a quaternary ammonium salt of an organic polymer.

34. The polymer composition of claim 27 wherein the composition is stable.

35. The polymer composition of claim 27 further comprising a secondary organic polymer.

36. The polymer composition of claim 35 wherein the secondary organic polymer is a hydrophobic material.

37. The polymer composition of claim 36 wherein the hydrophobic material forms a continuous matrix and the hydrophilic amine-containing polymer forms a discontinuous phase.

38. The polymer composition of claim 37 wherein the hydrophilic discontinuous phase is in the form of microparticles having an average particle size of 10 microns or less when in a substantially nonhydrated form.

39. The polymer composition of claim 37 which is a hydrocolloid.

40. The polymer composition of claim 39 comprising water in an amount of less than 1 weight percent, based on the total weight of the polymer composition.

41. The polymer composition of claim 36 wherein the hydrophobic material forms a discontinuous phase and the hydrophilic amine-containing polymer forms a continuous matrix.

42. The polymer composition of claim 36 wherein the hydrophobic material is liquid at room temperature.

43. The polymer composition of claim 42 wherein the hydrophobic material is mineral oil.

44. The polymer composition of claim 36 wherein the hydrophobic material is solid at room temperature.

45. The polymer composition of claim 36 wherein the hydrophobic material comprises an elastomeric polymer.

46. The polymer composition of claim 45 wherein the elastomeric polymer is selected from the group consisting of a polyisoprene, a styrene-diene block copolymer, a natural rubber, a polyurethane, a polyether-block-amide, a poly-alpha-olefin, a (C1-

C20)acrylic esters of meth(acrylic) acid, an ethylene-octene copolymer, and combinations thereof.

47. The polymer composition of claim 36 further comprising a foaming agent.

48. The polymer composition of claim 47 wherein the foaming agent is a physical foaming agent.

49. The polymer composition of claim 36 wherein the composition is stable.

50. The polymer composition of claim 36 further comprising a swelling agent.

51. The polymer composition of claim 36 further comprising an additive selected from the group consisting of a plasticizer, a tackifier, a crosslinking agent, a stabilizer, an extruding aid, a filler, a pigment, a dye, a swelling agent, a foaming agent, a chain transfer agent, and combinations thereof.

52. The polymer composition of claim 51 wherein the additive is a filler comprising fibers.

53. The polymer composition of claim 27 in the form of an extruded film.

54. A medical article comprising the polymer composition of claim 1.

55. The medical article of claim 54 which is a wound dressing or a wound packing material.

56. A medical article comprising the polymer composition of claim 27.

57. The medical article of claim 56 which is a wound dressing or a wound packing material.

58. A medical article comprising the polymer composition of claim 35.

59. The medical article of claim 58 which is a wound dressing or a wound packing material.

60. A method of using a polymer composition comprising applying the polymer composition of claim 1 to a wound.

61. A method of using a polymer composition comprising applying the polymer composition of claim 27 to a wound.

62. A method of using a polymer composition comprising applying the polymer composition of claim 35 to a wound.

63. A method of making a polymer composition, wherein the method comprises:

combining an inverse emulsion comprising hydrophilic organic microparticles with water and a bioactive agent under conditions effective to distribute at least a portion of the bioactive agent in the hydrophilic organic microparticles, wherein the bioactive agent is selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof; wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water.

optionally adding a secondary organic polymer to the inverse emulsion comprising the microparticles and bioactive agent; and

optionally removing a substantial portion of the water.

64. The method of claim 63 further comprising subjecting the polymer composition to radiation.

65. The method of claim 63 further comprising extruding or molding the composition.

66. The method of claim 63 further comprising blending in a foaming agent.

67. The method of claim 66 wherein the foaming agent comprises thermally expandable microspheres.

68. The method of claim 67 further comprising processing the composition under conditions effective to expand the thermally expandable microspheres.

69. The method of claim 67 further comprising processing the composition under conditions that do not significantly expand the thermally expandable microspheres and subsequently exposing the extruded material to conditions effective to expand the thermally expandable microspheres.

70. A method of making a polymer composition, wherein the method comprises:

combining monomers for a hydrophilic organic polymer with a bioactive agent under conditions effective to polymerize the monomers and distribute at least a portion of the bioactive agent in the hydrophilic organic polymer, wherein the bioactive agent is selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof; wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water; and

optionally adding a secondary organic polymer to the hydrophilic organic polymer.

71. A wound dressing comprising an apertured, liquid permeable substrate and the composition of claim 1 wherein the composition is nonadherent.

72. A wound dressing comprising an apertured, liquid permeable substrate and the composition of claim 27 wherein the composition is nonadherent.

73. A wound dressing comprising an apertured, liquid permeable substrate and the composition of claim 35 wherein the composition is nonadherent.

INTERNATIONAL SEARCH REPORT

International Application No
:T/US2004/003755

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/22 A61L15/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, EMBASE, BIOSIS, COMPENDEX, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199140 Derwent Publications Ltd., London, GB; Class A96, AN 1991-291352 XP002289245 & JP 03 193047 A (COTECH KK) 22 August 1991 (1991-08-22)	27-53, 56-59, 61,62, 70,72,73
Y	abstract	1-73
X	US 3 685 993 A (MUKHERJEE JOAN M W) 22 August 1972 (1972-08-22) claim 1	27-53,70

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2004	02/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Winger, R

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 039 940 A (ROUNS CAMERON G ET AL) 21 March 2000 (2000-03-21) cited in the application column 1, line 50 - line 62 column 3, line 15 - column 4, line 57 claims; examples	27-53, 56-59, 61,62, 70,72,73
Y	DE 199 58 697 A (BASF AG) 7 June 2001 (2001-06-07) page 3, line 50 - line 55 claims 1,3	1-73
Y	US 4 340 043 A (SEYMOUR DONALD E) 20 July 1982 (1982-07-20) column 2, line 7 - line 20; claims 1,19	1-73
A	US 4 528 321 A (FLESHER PETER ET AL) 9 July 1985 (1985-07-09) cited in the application the whole document	

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 60-62 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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(74) Agents: **LAMBERT, Nancy, M.** et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SILVER COATINGS AND METHODS OF MANUFACTURE

(57) Abstract: A silver composition containing sparingly soluble silver compounds and a method of coating the composition on a substrate is disclosed.

WO 2005/056067 A1

SILVER COATINGS AND METHODS OF MANUFACTURE

BACKGROUND

While wounds heal more effectively in moist environments, bacterial infection poses increased risk. Use of antibiotics to treat bacterial infections can build bacterial resistance. Silver compounds are known to impart antimicrobial effects to a surface with minimal risk of developing bacterial resistance. Silver is delivered to the surface by sustained release of silver ions from the surface when in contact with moist environments, such as a wound bed.

Silver compositions, such as silver nitrate and silver sulfadiazine, are effective antimicrobials used in a variety of applications. However, they are typically not light stable, leave a stain on skin with which they come into contact, and in the case of silver nitrate, can be quickly depleted in an aqueous environment. Wound dressings containing silver antimicrobials include textiles coated with silver compositions, such as those described in U.S. Patent. No. 6,436,420; hydrocolloids prepared with silver-amine complexes, such as those described in U.S. Patent No. 6,468,521; silver chloride in a wound dressing matrix described in EP 272149; and silver alginate wound dressings described in US 2003/0021832.

Certain silver compounds, such as silver oxides and select silver salts, are both stable and antimicrobial but demonstrate low solubility in aqueous media. Attempts to coat substrates with such compounds have had limited success, leaving limited quantities of the antimicrobial silver compound on the substrate.

SUMMARY

The present invention is directed to a method of coating silver compounds on a medical article, such as a gauze, a nonwoven, a foam, and a hydrocolloid. The coated silver compositions are preferably stable. By this it is meant that the compositions are stable to at least one of the following types of radiation: visible light, ultraviolet light, electron beam, and gamma ray sterilization.

In one aspect, the present invention provides a method of coating silver compounds on a substrate, comprising combining a sparingly soluble silver-containing compound with an ammonium-containing compound to form a solution, coating the solution on a substrate, and drying the coated substrate. The solution can be formed

and/or coated at temperatures less than 40 °C. An oxidizing agent can also be added to the solution or the coated substrate.

In another aspect, a method of coating silver compounds on a substrate is provided, comprising combining silver oxide with ammonium carbonate to form a solution, coating the solution on a substrate, and drying the coated substrate. The silver oxide is essentially the only compound that remains on the substrate after drying the substrate, with essentially all of the ammonium-containing compound removed after drying the substrate. An oxidizing agent can also be added to the solution or the coated substrate.

In another aspect, the silver compound can be coated on a substrate such as a nonwoven gauze, a woven gauze, a polyester fiber, a foam, a film and a hydrocolloid. In another aspect, an article is provided that is impregnated with a sparingly soluble silver-containing compound and essentially free of either the ammonium compound or residual components of the ammonium compound and the silver-containing compound.

In another aspect, a method of coating silver compounds on a substrate is provided, comprising combining silver oxide with an ammonium-containing compound to form a solution, adding an oxidizing agent in an effective amount to increase the valence state of the silver oxide, coating the solution on a substrate, and drying the coated substrate.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably. Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides a method for coating sparingly soluble silver compounds, such as silver oxides and silver salts, by dissolving silver compounds and ammonium salts in an aqueous solution, coating the solution on a substrate, and drying the coated substrate. The ammonium salts complex with the sparingly soluble silver

compounds to allow dissolution in water. Sparingly soluble as used herein can generally be defined as a silver compound concentration in solution of at least 1 μg/gram in water but less than 0.1 g per liter of water.

The process can be accomplished as a continuous process, can be done in a single step or with a single coating solution. The process to apply the coating does not require elevated temperatures, and can be applied at temperatures less than 40 °C, and preferably ambient or room temperature, e.g., 23 °C. The coating solution can be maintained below a pH of 13, and preferably less than 10, to minimize adverse effects to the substrate.

Sparingly soluble silver compounds provide sustained release of silver ions over time based in part on their limited solubility and inherent dissociation equilibrium constants. Silver compounds useful in the present invention include silver oxide, silver sulfate, silver acetate, silver chloride, silver lactate, silver phosphate, silver stearate, silver thiocyanate and silver carbonate. In a preferred embodiment, the silver compound is silver oxide.

The sparingly soluble silver compounds are dissolved in solution by complexing the silver compound with an ammonium salt. Suitable ammonium salts include ammonium pentaborate, ammonium acetate, ammonium carbonate, ammonium peroxyborate, ammonium tertraborate, triammonium citrate, ammonium carbamate, ammonium bicarbonate, ammonium malate, ammonium nitrate, ammonium nitrite, ammonium succinate, ammonium sulfate, ammonium tartarate, and mixtures thereof. Depending on the silver compound chosen, the silver compound may dissolve easily at room temperature, or may require mechanical action such as stirring over time to aid dissolution when heat is not applied.

The resultant solution containing the silver compound complexed with the ammonium salt can be coated on a substrate, typically an absorbent substrate. The coated substrate is dried to drive off the ammonia and other residual components, such as water and carbon dioxide, for example. Drying can be accomplished at room temperature or by heating the coated substrate. Heat will speed the drying process. In a preferred embodiment, the coated substrate is dried at temperatures below 200 °C, and more preferably below 160 °C, to minimize decomposition of the silver compounds.

Once dried, the substrate remains coated with the silver compound. The coated substrates are essentially free of silver metal, i.e., Ag(0). In some embodiments, the

choice of starting materials results in a coating that leaves no residue with essentially only the silver compound remaining on the substrate, and all other components of the silver solution removed from the substrate upon drying. Preferably, the silver solution is formed from the combination of silver oxide and ammonium carbonate. After coating, ammonia and carbon dioxide are driven off, leaving only the silver oxide remaining on the substrate.

In some embodiments, a higher valence silver oxide, i.e., where the oxidation state of silver is Ag (II), or Ag(III), can be used. The valence state of the silver coated on the substrate can be determined by use of the starting silver oxide material, i.e., AgO, Ag_2O, Ag_2O_3, Ag_2O_4. Alternatively, the valence state of the silver oxide can be increased by the addition of an oxidizing agent to the complexed silver oxide/ammonium salt solution or to the substrate after coating the solution. Suitable oxidizing agents include hydrogen peroxide and alkali metal persulfates such as sodium persulfate, as discussed in U.S. Patent No. 6,436,420 to Antelman. Other suitable oxidizing agents include permanganates, hypochlorites, perchlorates, and nitric acid.

When applied, the silver solution penetrates and impregnates the interior of the substrate. For example, when gauze is used, the silver solution impregnates between the fibers of the gauze. Similarly, when foam is used as the substrate, the silver solution impregnates the foam cells by both capillary action and absorption into the foam.

The concentration of silver compound on the substrate is a function of the silver compound in solution and the total amount of solution applied onto a unit area of the substrate. The silver compound concentration on the substrate is typically less than 10 mg/cm^2. In a preferred embodiment, the silver compound concentration on the substrate ranges from 0.1 mg/cm^2 to 2 mg/cm^2.

The silver compositions, once coated, are preferably stable. By this it is meant that the compositions are stable to at least one of the following types of radiation: visible light, ultraviolet light, electron beam, and gamma ray sterilization. In certain embodiments, the coated compositions are stable to visible light, such that the coated compositions do not darken upon exposure to visible light. Such compositions are useful in medical articles, particularly wound dressings and wound packing materials, although a wide variety of other products can be coated with the silver compositions. Wound dressings containing hydrocolloids can be used in their hydrated or swollen forms if desired.

Articles can be prepared using the silver solution described herein according to a variety of coating methods. When a porous substrate is coated, the process used typically allows the yarns, filaments, or film such as perforated or microporous film, to be coated, while leaving most of the apertures unobstructed by the composition. Depending on the structure of the support used, the amount of solution employed will vary over a wide range.

According to a variant of this process, a substrate can be passed through a bath of the silver composition. The substrate covered with the silver composition is then dried, for example in an oven at a temperature sufficient to evaporate constituents of the solution. The temperature is preferably at least 100 °C.

The silver solution can also be coated onto a carrier web or a backing (described below) using a known coating technique such as gravure coating, curtain coating, die coating, knife coating, roll coating, or spray coating. A preferred coating method is gravure coating.

If desired, compositions of the present invention can be sterilized. Methods of sterilization include treatment with electron beam or gamma radiation.

MEDICAL ARTICLES

The silver compositions of the present invention can be used in a wide variety of products, although they are preferably used in medical articles. Such medical articles can be in the form of a wound dressing, wound packing material, or other material that is applied directly to or contacts a wound. Other potential products include clothing, bedding, masks, dust cloths, shoe inserts, diapers, and hospital materials such as blankets, surgical drapes and gowns.

The silver compositions can be coated on various backings (i.e., a support substrate). The backing or support substrate can be porous or nonporous. The composition of the present invention can be coated on the support substrate or impregnated into it, for example.

Suitable materials are preferably flexible, and may be fabric, non-woven or woven polymeric webs, polymer films, hydrocolloids, foam, metallic foils, paper, and/or combinations thereof. More specifically, cotton gauze is useful with the silver compositions of the present invention. For certain embodiments it is desirable to use a permeable (e.g., with respect to moisture vapor), open apertured substrate (i.e., a

scrim). For certain embodiments it is desirable to use an open- or closed-cell foam, such as that disclosed in U.S. Patent No. 6548727. For certain embodiments, the substrate may be a hydrocolloid, such as a hydrophilic polymer, or hydrophobic polymer matrix containing hydrophilic particles, as described in applicants' copending applications, Ser. No. 10/728,577, and Ser. No. 10/728,439.

The substrates (i.e., backings) are preferably porous to allow the passage of wound fluids, moisture vapor, and air. In certain embodiments, the substrates are substantially impervious to liquid, especially wound exudate. In certain embodiments, the substrates are capable of absorbing liquid, especially wound exudate. In certain embodiments, the substrate is an apertured liquid permeable substrate.

Suitable porous substrates include knits, wovens (e.g., cheese cloth and gauze), nonwovens (including spun-bonded nonwovens, and BMF (blown micro fibers), extruded porous sheets, and perforated sheets. The apertures (i.e., openings) in the porous substrates are of sufficient size and sufficient number to facilitate high breathability. For certain embodiments, the porous substrates have at least 1 aperture per square centimeter. For certain embodiments, the porous substrates have no greater than 225 apertures per square centimeter. For certain embodiments, the apertures have an average opening size (i.e., the largest dimension of the opening) of at least 0.1 millimeter (mm). For certain embodiments, the apertures have an average opening size (i.e., the largest dimension of the opening) of no greater than 0.5 cm.

For certain embodiments, the porous substrates have a basis weight of at least 5 grams/meter^2. For certain embodiments, the porous substrates have a basis weight of no greater than 200 grams/meter^2.

The porous substrates (i.e., backings) are preferably flexible yet resistant to tearing. For certain embodiments, the thickness of the porous substrates is at least 0.0125 mm. For certain embodiments, the thickness of the porous substrates is no greater than 3 mm.

Materials of the backing or support substrate include a wide variety of materials including paper, natural or synthetic fibers, threads and yarns made from materials such as cotton, rayon, wool, hemp, jute, nylon, polyesters, polyacetates, polyacrylics, alginates, ethylene-propylene-diene rubbers, natural rubber, polyesters, polyisobutylenes, polyolefins (e.g., polypropylene polyethylene, ethylene propylene copolymers, and ethylene butylene copolymers), polyurethanes (including polyurethane

foams), vinyls including polyvinylchloride and ethylene-vinyl acetate, polyamides, polystyrenes, fiberglass, ceramic fibers, and/or combinations thereof.

The backing can also be provided with stretch-release properties. Stretch-release refers to the property of an adhesive article characterized in that, when the article is pulled from a surface, the article detaches from the surface without leaving significant visible residue. For example, a film backing can be formed from a highly extensible and highly elastic composition that includes elastomeric and thermoplastic A-B-A block copolymers, having a low rubber modulus, a lengthwise elongation to break of at least 200%, and a 50% rubber modulus of not above 2,000 pounds/square inch (13.8 megapascals (MPa)). Such backings are described in U.S. Pat. No. 4,024,312 (Korpman). Alternatively, the backing can be highly extensible and substantially non-recoverable such as those described in U.S. Pat. No. 5,516,581 (Kreckel et al,).

In certain embodiments, the coated substrates of the present invention are nonadherent, although it should be understood that an adhesive (e.g., a pressure sensitive adhesive) could be added to an article coated with the solution. As used herein, the silver compositions of the present invention when coated on a substrate do not adhere significantly to wound tissue such that they do not cause pain and/or destruction of the wound tissue upon removal and display a 180° peel strength of less than 1 N/cm from steel, as described in applicants' copending application, Ser. No. 10/729,114.

In certain embodiments, substrates coated with the silver composition can be covered on one or both sides by a permeable nonadherent outside layer to reduce adhesion and attachment to the wound. The nonadherent layer can be attached to the substrate, such as by coating or laminating. Alternatively, the coated substrate can be enclosed within a nonadherent layer, such as sleeve. The nonadherent layer can be made from nonadherent woven or nonwoven fabrics such as nylon or perflourinated-material coatings on cotton gauze. The nonadherent layer prevents attachment of materials from the enclosed silver coated substrate. At the same time, the nonadherent layer does not adversely affect the sustained release of silver from the coated substrate.

In another embodiment, the backing or support substrate can be composed of nonadherent material. For example, a nonadherent hydrophilic polymer can be used as the backing or support material, or coated on a permeable porous substrate, as

described in applicants' copending applications, Ser. No. 10/728,577; Ser. No. 10/729,114; and Ser. No. 10/728,439.

If desired, the coated substrate can be covered with two protective films (for example, thin polyester films). These films optionally may include a nonstick treatment and can function to facilitate extraction from a package and in handling the article. If desired, the coated substrate can be cut into individual compresses, of sizes suitable for the use, packaged in sealed sachets, and sterilized.

Pressure sensitive adhesives used in medical articles can be used in articles of the present invention. That is, a pressure sensitive adhesive material could be applied to the article of this invention, for example, around the periphery, to adhere the article to the skin.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention. All percentages are in weight percent unless specified otherwise.

Materials

Silver (I) Oxide (Ag_2O), Formula Weight (FW) is 231.7, available from Alfa Aesar, Ward Hill, Massachussetts.

Silver (II) Oxide (AgO), Formula Weight (FW) is 123.9, available from Alfa Aesar, Ward Hill, Massachussetts.

Silver sulfate, Formula Weight (FW) is 311.8, available from Alfa Aesar, Ward Hill, Massachussetts.

Trypticase (Tryptic) Soy Broth (TSB) medium available from Becton Dickinson & Company, Bedford, Massachusetts.

Polyester Knitted Fabric, a 24 mesh polyester knit (1.8 oz/sq yard) purchased from Lamports Filter Media, Inc, Cleveland, OH.

Ammonium carbonate, available from Mallinkrodt Baker, Inc., Phillipsburg, New Jersey.

Ammonium pentaborate, available from Mallinkrodt Baker, Inc., Phillipsburg, New Jersey.

Cotton nonwoven, 80 g/m^2, available from Cotton Incorporated, Cary, North Carolina.

Woven cotton, available from American Fiber and Finishing, Albermarle, North Carolina.

KRATON D1124K- radial 4-arm star polystyrene-polyisoprene $(SI)_4$ thermoplastic elastomeric copolymer having 30 wt-% polystyrene, available from KRATON Polymers, Houston, Texas.

SALCARE SC95- polymerized methylchloride quaternary ammonium salt of dimethylaminoethylmethacrylate (DMAEMA) dispersed in mineral oil and proprietary non-ionic surfactant, available from Ciba Specialty Chemicals, High Point, North Carolina.

SALCARE SC91 - polymerized sodium acrylate dispersed in mineral oil and proprietary non-ionic surfactant, available from Ciba Specialty Chemicals, High Point, North Carolina.

KAYDOL - mineral oil available from Crompton Corporation, formerly Witco Corporation.

IRGANOX 1010 -Phenolic antioxidant available from Ciba Specialty Chemicals, Tarrytown, New York.

Open cell polyurethane foam, available from 3M, St. Paul, Minnesota.

Antimicrobial Performance Tests

2 Hours % Live Bacteria Test

The effectiveness of a sample was tested using a L-7012, Bacterial Viability Kit, available from Molecular Probes (Eugene, Oregon). The procedure is outlined below using the red, propidium iodide dye, and green, SYTO 9 dye, contained in the kit to stain the live and dead bacteria.

Preparation of bacteria solution: Staphylococcus aureus bacteria and E. coli were grown in Trypticase (Tryptic) Soy Broth (TSB) medium overnight. Bacteria were concentrated by centrifugation at 10,000 x gravity for 15 minutes (min). Supernatant was removed and the pellet was re-suspended in MilliQ water (filtered through a 0.2 μm pore-size filter) or in Butterfield phosphate buffer (from Hardy Diagnostics, Santa Maria, California). Bacteria solution was diluted to the desired bacteria concentration (10^7 cells/milliliters) by measuring the optical density (OD) at 670 nm. For a control

experiment, the bacteria solution was incubated with 70% isopropyl alcohol at room temperature for 1 hour (hr) to measure the killed bacteria control. Different volume of live and dead bacteria solutions were mixed to generate a range of percent live solution for calibration purposes.

Sample preparation: All prototypes were prepared by punching out a 0.125 inch(.05 cm) to 1-inch (2.54-cm) diameter samples using a stainless steel punch; sometimes as indicated in the examples a 1-inch (2.54 cm) disk was further cut with scissors in eighths and then evaluated. The amount of sample was weighed, and then transferred to 50 milliliters (mL) sterile conical tubes.

Bacteria labeling and Antimicrobial testing: 7 mL of bacteria solution at initial concentration of approximately $1x10^8$ bacteria/mL were pipetted into a 50 mL conical tube containing the sample. At the specified time (e.g., 2 hr), 50 micro-liter (μL) of the supernatant was pipetted into fluorescent measurement tube which already contained 450 μL of MiliQ water and premixed green dye and red dye solution (1.5 μL dye mixture for 500 μL bacteria solution) was added and the mixture was incubated for 15 minutes in the dark at room temperature. These solutions were then measured by flow cytometry. Cell viability was measured using the BD FACSCaliber flow cytometer (made by Becton Dickinson & Company, Franklin Lakes, New Jersey). The flow cytometer is equipped with an argon-ion laser at 488 nanometers (nm) and 15 milliWatts (mW) output. Data acquisition and analysis were controlled using CellQuest software and PBPAC hardware interface. The light path contained a 488/10 nm blocking filter, then a 530/30 nm filter before the green PMT and a 585/42 nm long pass filter before the red PMT. The sampling rate was around 3000-7000 particles/second. The sheath fluid was FACSFlow by Becton Dickinson. The instrument voltage was 5.5 Volt.

The live cell and dead bacteria responses were established with the 100 % live cell and 100% dead cell (for killed bacteria, bacteria solution was incubated with 70% isopropyl alcohol at room temperature for 1 hr) samples. Different volumes of live and dead bacteria solutions were mixed to generate a range of percent live solutions for calibration purposes. The sample results for bacteria killing ability were interpolated from the standard curve generated from calibration samples. Total bacteria concentration was determined by the measuring of the OD at 670 nm of the bacteria solution.

Zone of Inhibition Test

Antimicrobial performance was measured using a Zone of Inhibition test (ZOI) that was performed by the following method. Mueller-Hinton agar was prepared, sterilized and tempered in a water bath at 48-50°C. A suspension of bacteria in sterile phosphate-buffered water was prepared with approximately 10^8 CFU/ml. The agar was inoculated with a bacterial suspension of bacteria to an approximate concentration of 10^5 CFU/ml (1:1000). The inoculated agar was swirled to mix and pipetted (~14 ml) into sterile Petri dishes (15 x 100 mm). The seeded agar was allowed to set for about 20 minutes to harden. An alcohol-disinfected die and cutting board were used to cut textile samples to desired size. Sterile forceps were used to place the samples onto the seeded, hardened agar in center of plate. The plate was then placed into an incubator at 35-37°C for overnight (16-24 hours) incubation. After incubation the clear zones, where no visible colonies formed, were measured in mm with calipers.

The zone of inhibition (ZOI) is then calculated by the following equation

ZOI = [diameter of clear zone (mm) – diameter of sample (mm)]/2

Saline Absorbency Test

Samples were soaked in .85% by weight sodium chloride solution (saline). The samples were removed from the saline at various times and were lightly dabbed with a paper towel. The weight was recorded. The weight of saline absorbed per weight of dry coating was calculated using the following equation: (weight saline absorbed) = [(saline swollen weight) – (dry sample weight)]/(dry sample weight) .

Example 1

A clear solution of 1% silver (II) oxide and 5% ammonium carbonate in water was prepared by stirring the mixture until the silver (II) oxide was fully dissolved. A 7.62x5.08 cm nonwoven cotton gauze was dipped in the solution for five seconds, removed and patted with a paper towel to remove excess solution. The coated gauze was then dried in a 150°C oven for ten minutes. After drying, the gauze turned a deep brown color.

When dipped in saline, the cotton gauze coated with silver oxide absorbed 4.89 grams saline per gram dressing. As a comparison, a cotton gauze sample without silver oxide coating absorbed 4.75 grams saline per gram dressing.

Zone of Inhibition tests were run on three 7 mm samples of the silver oxide-coated cotton gauze over 9 days. At the end of each 24-hour period, the samples were evaluated, removed from the agar plate and transferred to a freshly inoculated agar plate.

Zone of Inhibition results are shown in Table 1 below:

TABLE 1

Day	ZOI (mm)	Growth under the sample disc
1	3	None
2	2	None
3	2	None
4	1.5	None
5	1.5	None
6	1.5	None
7	.5	None
8	0	Slight
9	0	Moderate

Example 2

A solution of 30 parts of silver (I) oxide, 100 parts ammonium carbonate, and 2870 parts water were mixed in a glass jar until the silver (I) oxide was completely dissolved. The solution was gravure coated at 100 g/m^2 at 1.6 m/min on a nonwoven cotton. The coated nonwoven cotton was heated in an oven at 160 °C for 5 minutes. The dry coating was light brown.

Example 3

The solution was prepared as in Example 2 except that the solution was coated on woven cotton. After microwave digestion of the woven cotton gauze, analysis by an ion chromatograph (model, source) showed no detectable ammonium ion.

Zone of Inhibition tests were run on three layers of 10 mm sample. The ZOI after 24 hours was 3.75 for S. aureus and 2.85 for E. coli.

Example 4

Same as Example 2 except that the solution was coated on a polyester knit. The dried coating was light grey.

Example 5

Same as Example 2 except that silver (II) oxide was used.

Example 6

Nonwoven cotton gauze was dipped in a solution comprising 1% Ag_2O and 5% ammonium pentaborate in water. Excess solution was squeezed from the dipped gauze, and the gauze was weighed. The total solution weight absorbed by the gauze sample was 2.5 grams. When divided by the area of the gauze, the total solution uptake was 0.024 grams/cm^2. The silver compound concentration on the gauze was 0.24 mg/cm^2.

The gauze was dried in 150°C oven for 10 minutes. After drying, the gauze turned dark brown in color. The ZOI after 24 hours was 1.5 mm.

Example 7

Nonwoven cotton gauze was dipped in a solution comprising 2% silver carbonate, 5% ammonium acetate and 1.5% ammonia with the balance water. Excess solution was squeezed from the dipped gauze, and the gauze was weighed. The total solution weight absorbed by the gauze sample was 2.24 grams. When divided by the area of the gauze, the total solution uptake was 0.028 grams/cm^2. The total silver compound concentration on the gauze was 0.56 mg/cm^2.

The gauze was dried in 150°C oven for 10 minutes. After drying, the gauze turned medium brown in color. The ZOI after 24 hours was 2 mm.

Example 8

Polyurethane foam was dipped in a solution comprising 1% silver (II) oxide (AgO) and 5% ammonium carbonate in water. Excess solution was squeezed from the dipped foam, and the foam was weighed. The total solution weight absorbed by the

foam sample was 6 grams. When divided by the area of the sample, the total solution uptake was 0.095 grams/cm^2. The total silver compound concentration on the gauze was 0.95 mg/cm^2.

The foam was dried in 120°C oven for 10 minutes. After drying, the foam turned brown in color. The ZOI after 24 hours was 2 mm.

Example 9

Polyurethane foam was dipped in a solution comprising 1% silver sulfate and 5% ammonium carbonate in water. Excess solution was squeezed from the dipped foam, and the foam was weighed. The total solution weight absorbed by the foam sample was 3.2 grams. When divided by the area of the sample, the total solution uptake was 0.051 grams/cm^2. The total silver compound concentration on the foam was 0.51 mg/cm^2.

The foam was dried in 120°C oven for 10 minutes. After drying, the foam turned brown in color. The ZOI after 24 hours was 1.5 mm.

Example 10

Woven cotton gauze was ink jet coated with a solution comprising 4% THV 200 fluorothermoplastic (available from Dyneon, LLC, Oakdale, Minnesota) in Methyl-ethyl ketone solution (available from Sigma Aldrich, Milwaukee, Wisconsin) using the Xaar XJ128-200 piezo printhead (Available form Xaar Ltd., Cambridge, England) at 300x300 dpi.

Nonadherency of the coated gauze was evaluated using a 2 inch piece of Scotch™ Magic Tape (available from 3M, St. Paul, Minnesota) by applying the tape to the coated gauze, rolling once, and removing by hand. The tape removed easily without pulling fibers. Gauze without the THV coating resisted pull, and fibers were pulled off when the tape was removed.

The gauze coated with silver solution of Example 1 was placed between the THV coated gauze and sealed at the edges using double-stick tape. The silver-nonadherent gauze construction absorbed 3.28 grams of saline. Using 7 mm samples of the gauze construction, the ZOI after 24 hours was 2.5 mm.

Example 11

The coated gauze of Example 1 was placed between two sheets of woven 100% nylon fabric (available from JoAnn Fabrics, Woodbury, Minnesota) and sealed at the edges using double-stick tape. The silver-nylon gauze construction absorbed 3.46 grams of saline. Using 7 mm samples of the construction, the ZOI after 24 hours was 1.5 mm.

Example 12

A hydrocolloid dressing, under the trade name Tegasorb™ (available from 3M, St. Paul, Minnesota) was dipped in a clear silver solution prepared with 100 parts of silver (I) oxide, 337 parts of ammonium carbonate, and 3000 parts of de-ionized water. The dressing was soaked in the silver solution for two minutes, contacting only the hydrocolloid material. The coated hydrocolloid substrate was placed in an oven at 100 °C for 30 minutes.

The coated dressing was tested using the % Live Bacteria Test. Samples having a diameter of 12.7 mm were placed in contact with 7 mls of bacterial solution having approximately 10^8 counts of S. aureaus. At 30 minutes the % Live results were 60.5, and at 2 hours the % Live results were 0.72.

Example 13

A nonadherent hydrocolloid dressing was prepared based on a Styrene-isoprene-styrene gel and SALCARE SC91 hydrocolloid. KRATON D1124K styrene-isoprene-styrene (SIS) pellets were gravimetrically fed into the feed throat (barrel section 1) of a Werner Pfleiderer ZSK30 co-rotating twin-screw extruder (TSE) having a 30 mm diameter and 15 barrel sections.

Each temperature zone was a combination of two barrel sections (e.g., Zone 1 corresponded to barrel sections 2 and 3). Barrel section 1 was controlled at full cooling capacity for all SIS gel lots. A powdered antioxidant (IRGANOX 1010) was also gravimetrically fed into barrel section 1. KAYDOL mineral oil was heated and added to the TSE as described in International Publication No. WO 97/00163. The disclosed compounding process provides a method for making a gel by melting of the SIS elastomer followed by addition of the heated mineral oil. Heated mineral oil was sequentially injected into barrel sections 4, 6, 8, 10 and 12, respectively. The TSE

screw speed was controlled to 400 revolutions per minute (rpm). The TSE temperature profile was controlled to 204°C, 227°C, 227°C, 204°C, 182°C, 171°C, and 93°C for zones 1-7, respectively. The heated oil injections were controlled to 204°C, 204°C, 204°C, 177°C, and 177°C, respectively. Table 2 contains the material flow rates and Table 3 contains the compositional information for the SIS gel.

Table 2. SIS gel flow rates

SIS (g/min)	Barrel Section(S) and Oil addition number and Rate (g/min)					Total KAYDOL Oil (g/min)	IRGANOX 1010 (g/min)	Total Flow Rate (g/min)
	S4 Oil 1	S6 Oil 2	S8 Oil 3	S10 Oil 4	S12 Oil 5			
227	74	100	120	120	108	522	8	757

Table 3. SIS gel composition

SIS Type	SIS (wt-%)	KAYDOL oil (wt-%)	IRGANOX 1010 (wt-%)
Radial	30.0	69.0	1.0

The pre-compounded SIS gel was combined with SALCARE SC91 in a Haake 25 mm diameter, fully intermeshing counter-rotating TSE. The SIS gel was re-melted in a Bonnot extruder operating at 127°C, and injected at 22.8 grams per minute into barrel section 2 of the TSE. SALCARE SC91 inverse emulsion was injected at ambient temperature into barrel section 4 at 15.2 grams per minute (g/min) using a Zenith gear pump. The TSE was controlled at 300 rpm screw speed and 121°C temperature. The total material throughput was 38.0 grams per minute. The SIS gel/SALCARE SC91 blend was discharged out of the TSE into a transport hose using a Zenith gear pump. A transport hose conveyed the molten gel blend to a 0.15meter (m) wide single orifice film die. The transport hose and die were both controlled to 121°C. The molten gel blend was extruded into a nip formed by two gapped and polished steel

rolls controlled to 110°C. A polyester (PET) knitted fabric having 0.8 mm by 0.7 mm (0.56 mm^2) rectangular open apertures, 0.20 millimeter (mm) thickness and 0.15 meter (m) width was also fed into the nip at 1.4 m/min speed. As the fabric exited the nip, the gel-coated article was cooled in air before being wound up with an inserted paper release liner. After air-cooling to ambient temperature a coated fabric having 0.75 mm by 0.6 mm (0.45 mm^2) rectangular open apertures was obtained. Table 4 contains the process conditions and Table 5 contains the compositional information for the dressing:

Table 4. Process conditions

SIS Gel Input (barrel section number)	SALCARE Input (barrel section number)	Steel Roll Gap (mm)	Coating Speed (m/min)	Coating Weight (g/m^2)
2	4	0.25	2.1	78

Table 5. Composition

SIS (wt-%)	IRGANOX 1010 (wt-%)	SALCARE SC91 (wt-%)	KAYDOL oil (wt-%)
18.0	0.6	40.0	41.4

The nonadherent dressing was dipped in a clear silver solution prepared with 100 parts of silver (I) oxide, 337 parts of ammonium carbonate, and 3000 parts of de-ionized water. The dressing was soaked in the silver solution for two minutes, contacting only the hydrocolloid material. The coated hydrocolloid dressing was placed in an oven at 100 °C for 30 minutes.

The coated dressing was tested using the % Live Bacteria Test. Samples having a diameter of 12.7 mm were placed in contact with 7 mls of bacterial solution having approximately 10^8 counts of S. aureaus. At 30 minutes the % Live results were 0.92, and at 2 hours the % Live results were 0.04.

Example 14

A solution of 1.3% silver (I) oxide, 4.4% ammonium carbonate, and 94.3% water were mixed in a glass jar until the silver(I) oxide was completely dissolved. The

solution was gravure coated at 100 g/m^2 at 1.6 m/min on a nonwoven cotton. The coated nonwoven cotton was heated in an oven at 160 °C for 5 minutes.

The coated dressing was tested using the % Live Bacteria Test. Samples having a diameter of 12.7 mm were placed in contact with 7 mls of bacterial solution having approximately 10^8 counts of S. aureaus. At 30 minutes the % Live results were 2.91, and at 2 hours the % Live results were 0.07.

WHAT IS CLAIMED IS:

1. A method of coating silver compounds on a substrate, the method comprising:

combining a sparingly soluble silver-containing compound with an ammonium-containing compound to form an aqueous solution,

coating the solution on a substrate,

and drying the coated substrate.

2. The method of claim 1, wherein the solution has a pH of about 9.

3. The method of claim 1 wherein the solution is formed at less than 40 °C.

4. The method of claim 1, wherein the solution is coated at less than 40 °C.

5. The method of claim 1, wherein the silver-containing compound is selected from the group consisting of silver chloride, silver sulfate, silver carbonate, silver oxide, silver stearate, silver phosphate, and silver thiocyanate.

6. The method of claim 5 wherein the silver-containing compound is silver oxide.

7. The method of claim 1, wherein the ammonium-containing compound is selected from the group consisting of ammonium carbonate, ammonium pentaborate and ammonium acetate.

8. The method of claim 7 wherein the ammonium-containing compound is ammonium carbonate.

9. The method of claim 1, wherein the silver-containing compound forms a silver-ammonium complex when combined with the ammonium-containing compound.

10. The method of claim 1, wherein the silver-containing compound remains on the substrate after drying the substrate while the remainder of the coating is volatilized.

11. The method of claim 1, wherein the ammonium-containing compound is essentially all removed after drying the substrate.

12. The method of claim 1, further comprising the step of adding an oxidizing agent to the solution.

13. The method of claim 1, further comprising the step of adding an oxidizing agent to the coated substrate.

14. The method of claim 1, wherein the substrate is selected from the group consisting of a nonwoven gauze, a woven gauze, a polyester fiber, a foam, a film and a hydrocolloid.

15. A method of coating silver compounds on a substrate, the method comprising:
combining silver oxide with ammonium carbonate to form an aqueous solution,
coating the solution on a substrate,
and drying the coated substrate.

16. The method of claim 15, wherein the solution has a pH of about 9.

17. The method of claim 15, wherein the solution is formed at less than 40 °C.

18. The method of claim 15, wherein the solution is coated at less than 40 °C.

19. The method of claim 15, wherein the silver oxide forms a silver-ammonium complex when combined with the ammonium carbonate.

20. The method of claim 15, wherein the silver oxide is the only compound from the solution that remains on the substrate after drying the substrate.

21. The method of claim 15, wherein the ammonium carbonate is removed after drying the substrate.

22. The method of claim 15, further comprising the step of adding an oxidizing agent to the solution.

23. The method of claim 15, further comprising the step of adding an oxidizing agent to the coated substrate.

24. The method of claim 15, wherein the substrate is selected from the group consisting of a nonwoven gauze, a woven gauze, a polyester fiber, a foam, a film and a hydrocolloid.

25. An article made by the method of claim 1 wherein the article impregnated with sparingly soluble silver-containing compound is essentially free of the ammonium compound or residual components of the ammonium compound and the silver-containing compound introduced during the application of the solution.

26. An article made by the method of claim 15 wherein the article impregnated with silver oxide is essentially free of compounds introduced during the application of the solution other than the silver oxide.

27. A method of coating silver compounds on a substrate, the method comprising:

combining silver oxide with an ammonium-containing compound to form an aqueous solution,

adding an oxidizing agent in an effective amount to increase the valence state of the silver oxide,

coating the solution on a substrate,

and drying the coated substrate.

28. The method of claim 27, wherein the solution has a pH of about 9.

29. The method of claim 27, wherein the solution is formed at less than 40 °C.

30. The method of claim 27, wherein the solution is coated at less than 40 °C.

31. The method of claim 27, wherein the ammonium-containing compound is selected from the group consisting of ammonium carbonate, ammonium pentaborate and ammonium acetate.

32. The method of claim 31 wherein the ammonium-containing compound is ammonium carbonate.

33. The method of claim 27, wherein the silver oxide forms a silver-ammonium complex when combined with the ammonium-containing compound.

34. The method of claim 27, wherein the silver oxide is the only compound from the solution that remains on the substrate after drying the substrate.

35. The method of claim 27, wherein the substrate is selected from the group consisting of a nonwoven gauze, a woven gauze, a polyester fiber, a foam, a film and a hydrocolloid.

36. The method of claim 1, wherein the composition is stable.

37. A wound dressing made by the method of claim 1.

38. A wound dressing made by the method of claim 15.

39. A wound dressing made by the method of claim 27.

40. A medical article comprising a porous substrate impregnated with one or more sparingly soluble silver compounds, wherein the medical article has less than 1 N/cm peel strength to steel and does not adhere to wound tissue.

41. The medical article of claim 40, wherein the medical article is capable of absorbing saline in an amount of at least 100% of the article's dry weight.

42. The medical article of claim 40, wherein the medical article is capable of absorbing saline in an amount of at least 200% of the article's dry weight.

43. The medical article of claim 40, wherein the porous substrate is nonadherent.

44. The medical article of claim 40, wherein the porous substrate is covered on one or more sides by a nonadherent layer.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L15/44 C23C18/44 A61K31/28 A61K31/74 A61K33/38
A61L26/00 A61L27/54 A61L29/16 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 02/43743 A (BRISTOL-MYERS SQUIBB COMPANY; BOWLER, PHILIP; JACQUES, ELIZABETH; PARS) 6 June 2002 (2002-06-06) page 1, line 10 - line 26 page 5, line 19 - page 7, line 25 claims	1-44
X	US 4 652 465 A (KOTO ET AL) 24 March 1987 (1987-03-24) claims	1-24

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Thornton, S

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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(54) Title: WOUND DRESSINGS AND METHODS

(57) Abstract: A wound dressing that includes apertured, liquid permeable substrate and an absorbent, nonadherent polymer composition comprising: a hydrophobic organic polymer matrix; an optional plasticizing agent; and hydrophilic organic microparticles.

WOUND DRESSINGS AND METHODS

BACKGROUND

The wound healing process involves the growth of capillaries, fibroblasts, and epithelium into the wound site for building up new tissue. The newly formed tissue is extremely delicate and supersensitive to external influences. If a wound still in progress of regenerating tissue is covered with a dressing composed of a fibrous material, the fibers may easily intermingle with the newly formed tissues and give rise to inflammatory reactions in the wound tissue, which would result in deterioration of the wound healing process. Furthermore, the wound tissue would also be mechanically damaged in connection with removal and change of dressing. To avoid this, it is desirable that the dressing applied to the wound does not adhere to dried wound exudate, or in any coagulum formed.

Wound dressings intended for use during this particularly sensitive stage of the wound healing process are preferably designed so as not to stick to the wound bed. Also, it is desirable if they are pliable and have a soft wound-contacting surface. In addition, it is desirable if they are capable of absorbing excess amounts of wound exudate and/or to allow for the passage of wound exudate into an absorbent body placed over the dressing.

SUMMARY

The present invention is directed to polymer compositions that are useful in wound dressings.

In one aspect of the invention there are provided wound dressings. In one embodiment, a wound dressing includes an apertured liquid permeable substrate and an absorbent, nonadherent polymer composition that includes: a hydrophobic organic polymer matrix; an optional plasticizing agent; and hydrophilic organic microparticles. For certain embodiments, the plasticizing agent is present.

For certain embodiments, the hydrophobic polymer matrix includes a styrene-isoprene-styrene copolymer, a styrene-butadiene-styrene copolymer, or mixtures thereof. For certain embodiments, the hydrophobic polymer matrix includes a mixture of two or more polymers.

For certain embodiments, the microparticles when in a substantially nonhydrated form have an average particle size of 10 microns or less. For certain embodiments, the microparticles when in a substantially nonhydrated form have an average particle size of 1 micron or less. For certain other embodiments, the microparticles when in a substantially nonhydrated form have an average particle size of 0.5 micron or less.

For certain embodiments, the apertured liquid permeable substrate includes 1 to 225 apertures per square centimeter. For certain embodiments, the apertured liquid permeable substrate includes apertures having an average opening size of 0.1 millimeter to 0.5 centimeter.

For certain embodiments, the microparticles include an amine-containing organic polymer. For certain embodiments, the amine-containing organic polymer microparticles include a quaternary ammonium salt of an organic polymer. The microparticles include a cationic homopolymer of the methyl chloride quaternary salt of 2-(dimethylamino)ethyl methacrylate.

For certain embodiments, the microparticles include a copolymer of sodium acrylate and acrylic acid.

For certain embodiments, the microparticles are in the form of an inverse emulsion.

For certain embodiments, the microparticles are present in an amount of 1 wt-% to 60 wt-%, based on the total weight of the polymer composition.

For certain embodiments, the polymer composition further includes a bioactive agent, such as an antimicrobial agent. For certain embodiments, the polymer composition further includes an additive selected from the group consisting of a tackifier, a crosslinking agent, a stabilizer, a compatibilizer, an extruding aid, a filler, a pigment, a dye, a swelling agent, a chain transfer agent, and combinations thereof.

The present invention also provides a wound dressing that includes an apertured liquid permeable substrate and an absorbent, nonadherent polymer composition. The composition includes: a hydrophobic organic polymer matrix including a styrene-isoprene-styrene copolymer, a styrene-butadiene-styrene copolymer, or mixtures thereof; an optional plasticizing agent; and hydrophilic microparticles including an amine-containing organic polymer.

The present invention also provides a wound dressing that includes an apertured liquid permeable substrate and an absorbent, nonadherent polymer composition. The composition includes: a hydrophobic organic polymer matrix including a styrene-isoprene-styrene copolymer, a styrene-butadiene-styrene copolymer, or mixtures thereof; an optional plasticizing agent; and hydrophilic microparticles including a sodium polyacrylate copolymer.

The present invention also provides methods of treating a wound, the methods include comprising applying a wound dressing as described herein.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably. Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides wound dressings that include an apertured liquid permeable substrate and a polymer composition, which can be coated on or impregnated in the substrate. The polymer composition is absorbent and nonadherent and includes a hydrophobic organic polymer matrix, an optional plasticizer, and hydrophilic organic microparticles.

In the context of the polymer composition, the term "absorbent" means that the composition demonstrates a saline absorbency that is at least 50% of the dry weight of the polymer composition.

In the context of the polymer composition, the term "nonadherent" means that a composition of the present invention coated on a substrate displays a 180° peel strength of less than 1 Newton per centimeter (N/cm) from stainless steel according the to test procedure described in the Examples Section. Preferably, the compositions of the present invention do not adhere significantly to wound tissue such that they do not cause pain and/or destruction of the wound tissue upon removal. Although the composition itself is nonadherent, it should be understood that an adhesive (e.g., a

pressure sensitive adhesive) could be added to an article that includes the composition, if desired.

Typically, the hydrophobic organic polymer matrix forms a continuous matrix with the hydrophilic particles substantially uniformly dispersed therein. This dispersion is often referred to as a hydrocolloid. The hydrophobic organic polymer matrix contributes significantly to the nonadherency of the polymer composition, whereas the hydrophilic organic microparticles contribute significantly to the absorbency.

The hydrophilic microparticles can be prepared from a wide range of polymers, including anionic, cationic, amphoteric, non-ionic polymers, or combinations thereof. In a preferred embodiment, the hydrophilic microparticles include an amine-containing polymer, which is more preferably a cationic quaternary ammonium salt of an organic polymer. In another preferred embodiment, the hydrophilic microparticles include an anionic polyacrylate.

The compositions of the present invention are preferably light stable. By this it is meant that the compositions are stable to at least one of the following types of radiation: visible light; ultraviolet light; electron beam; and gamma ray sterilization.

As stated above, the polymer compositions of the present invention are absorbent. Wound dressings containing such compositions of the present invention can be used in their hydrated or swollen forms if desired. However, because the wound dressings include an apertured, liquid permeable substrate, the construction is prepared in such a way that the polymer composition can absorb fluid, yet in the swollen state, the apertures are not swollen shut. This allows fluid to traverse the dressing (perhaps into an overlying sorbent material, such as gauze) and not get trapped under it.

HYDROPHOBIC ORGANIC POLYMER MATRIX

The polymer compositions include a hydrophobic organic polymer matrix. In this context, "hydrophobic" means that the polymer matrix is antagonistic to, sheds, tends not to combine with, or is incapable of dissolving in water. Hydrophobic materials are particularly desirable for nonadherent compositions and articles.

Examples of hydrophobic materials include, but are not limited to, polyisobutylene, polyethylene-propylene rubber, polyethylene-propylene diene-modified rubber, polyisoprene, styrene-isoprene-styrene, styrene-butadiene-styrene,

styrene-ethylene-propylene-styrene, and styrene-ethylene-butylene-styrene. Particularly preferred hydrophobic materials include a styrene-isoprene-styrene copolymer and/or a styrene-butadiene-styrene copolymer, and even more preferred materials include a styrene-isoprene-styrene copolymer.

Other polymers (referred to herein as "optional secondary polymers") may also be included within the hydrophobic polymer matrix. The following are examples of such polymers.

Elastomeric polymers useful as optional secondary polymers in the invention are typically materials that form one phase at 21°C, have a glass transition temperature less than 0°C, and exhibit elastomeric properties. The elastomeric polymers include, but are not limited to, polyisoprenes, styrene-diene block copolymers, natural rubber, polyurethanes, polyether-block-amides, poly-alpha-olefins, (C1-C20)acrylic esters of meth(acrylic) acid, ethylene-octene copolymers, and combinations thereof. Elastomeric materials useful in the present invention include, for example, natural rubbers such as CV-60 (a controlled viscosity grade natural rubber having Mooney viscosity of 60 +/- 5 ML, 1+4 at 100°C, available as an International commodity); butyl rubbers, such as Exxon Butyl 268 available from Exxon Chemical Co., Houston, Texas; synthetic poly-isoprenes such as CARIFLEX IR309, available from Kraton Polymers, Houston, Texas, and NATSYN 2210, available from Goodyear Tire and Rubber Co., Akron, Ohio; ethylene-propylenes; polybutadienes; polyisobutylenes such as VISTANEX MM L-80, available from ExxonMobil Chemical Co.; and styrene-butadiene random copolymer rubbers such as AMERIPOL 1011A, available from BF Goodrich of Akron, Ohio.

Thermoplastic polymers useful as optional secondary polymers in the invention include, for example, polyolefins such as isotactic polypropylene; low density or linear low density polyethylene; medium density polyethylene; high density polyethylene; polybutylene; polyolefin copolymers or terpolymers, such as ethylene/propylene copolymer and blends thereof; ethylene-vinyl acetate copolymers such as ELVAX 260, available from E.I. DuPont de Nemours & Co., Wilmington, Delaware; ethylene acrylic acid copolymers; ethylene methacrylic acid copolymers such as SURLYN 1702, available from E. I. DuPont de Nemours & Co.; polymethylmethacrylate; polystyrene; ethylene vinyl alcohol; polyester; amorphous polyester; polyamides; fluorinated thermoplastics such a polyvinylidene fluoride; polytetrafluoroethylene; fluorinated

ethylene/propylene copolymers; halogenated thermoplastics such as a chlorinated polyethylene; and combinations thereof. Other exemplary thermoplastic polymers are disclosed in International Publication No. WO 97/23577. Preferably, the thermoplastic polymer is a polyolefin.

Thermoplastic elastomeric polymers useful as optional secondary polymers in the invention are typically materials that form at least two phases at 21°C, flow at a temperature greater than 50°C and exhibit elastomeric properties. Thermoplastic elastomeric materials useful in the present invention include, for example, linear, radial, star and tapered styrene-isoprene block copolymers such as KRATON D1107P, available from Kraton Polymers, and EUROPRENE SOL TE 9110, available from EniChem Elastomers Americas, Inc. Houston, Texas, linear styrene-(ethylene/butylene) block copolymers such as KRATON G1657 available from Kraton Polymers, linear styrene-(ethylene/propylene) block copolymers such as KRATON G1657X available from Kraton Polymers, styrene-isoprene-styrene block copolymers such as KRATON D1119P available from Kraton Polymers, linear, radial, and star styrene-butadiene block copolymers such as KRATON D1118X, available from Kraton Polymers, and EUROPRENE SOL TE 6205 available from EniChem Elastomers Americas, Inc., polyetheresters such as HYTREL G3548, available from E. I. DuPont de Nemours & Co., and poly-alpha-olefin based thermoplastic elastomeric materials such as those represented by the formula -(CH_2-CHR) where R is an alkyl group containing 2 to 10 carbon atoms and poly-alpha-olefins based on metallocene catalysis such as ENGAGE EG8200, an ethylene/l-octene copolymer available from DuPont Dow Elastomers Co., Wilmington, Delaware. Other exemplary thermoplastic elastomers are disclosed in International Publication No. WO 96/25469.

Various combinations of optional secondary organic polymers in various amounts can be used to produce desired effects. This can be readily determined by one of skill in the art based on the teachings herein.

ABSORBENT HYDROPHILIC MICROPARTICLES

The hydrophilic microparticles can include anionic, cationic, amphoteric, non-ionic polymers, or combinations thereof. Typically, the type and amount of microparticles are selected to provide the desired absorbency to the polymer composition of the present invention.

Preferably, the microparticles, when in a substantially nonhydrated form, have an average particle size of 10 microns or less, and more preferably, 1 micron or less. Typically and preferably, the microparticles have an average particle size of 0.5 micron or more when in a substantially nonhydrated form.

Preferably, the hydrophilic polymer has a weight average molecular weight of at least 1000.

Preferably, the polymer is also dermatologically acceptable and non-reactive with the skin of the patient or with other components of the composition including any antimicrobial agents that may be present in therein.

Hydrophilic microparticles useful in the present invention may be made from a wide variety of synthetically prepared polymers, naturally occurring polymers, or chemically modified naturally occurring hydrophilic polymers. Varieties of polymers that can be used include synthetic polymers prepared from single or multiple monomers. The microparticles can be in an emulsion, such as an inverse emulsion that includes absorbent hydrophilic microparticles. In certain embodiments, the microparticles can be in a dispersion.

Non-limiting examples of such polymers include: polyhydroxyalkyl acrylates and methacrylates (e.g., those prepared from 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, 2-hydroxypropyl acrylate, 2-hydroxypropyl methacrylate, 2,3-dihydroxypropyl methacrylate); poly(meth)acrylic acid and salts thereof (wherein (meth)acrylic acid refers to methacrylic acid and acrylic acid); polyvinyl lactams (e.g., those prepared from N-vinyl lactams such as N-vinyl-2-pyrrolidone, 5-methyl-N-vinyl-2-pyrrolidone, 5-ethyl-N-vinyl-2-pyrrolidone, 3,3-dimethyl-N-vinyl-2-pyrrolidone, 3-methyl-N-vinyl-2-pyrrolidone, 3-ethyl-N-vinyl-2-pyrrolidone, 4-methyl-N-vinyl-2-pyrrolidone, 4-ethyl-N-vinyl-2-pyrrolidone, N-vinyl-2-valerolactam, and N-vinyl-2-caprolactam); polyvinyl alcohols; polyoxyalkylenes; polyacrylamides; polystyrene sulfonates, natural or synthetically modified polysaccarides (e.g., starch, glycogen, hemicelluloses, pentosans, gelatin, celluloses, pectin, chitosan, and chitin), alginates, gums (e.g., Locust Bean, Guar, Agar, Carrageenan, Xanthan, Karaya, alginates, tragacanth, Ghatti, and Furcelleran gums), cellulosics (e.g., those prepared from methyl cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose, and hydroxypropyl cellulose); polymers prepared from water soluble amides (e.g., N-(hydroxymethyl)acrylamide and N-methacrylamide, N-(3-hydroxpropyl)acrylamide, N-

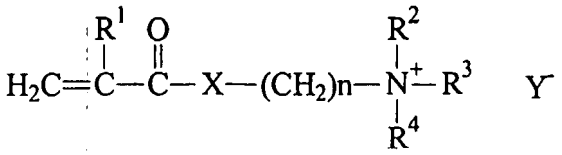
(2-hydroxyethyl) methacrylamide, N-(1,1-dimethyl-3-oxabutyl)acrylamide N-[2-(dimethylamine)ethylacrylamide and -methacrylamide, N-[3-(dimethylamino)-2-hydroxylpropyllmethacrylamide, and N-[1,1-dimethyl-2-(hydroxymethyl)-3-oxabutyllacrylamide)); polymers prepared from water-soluble hydrazine derivatives (e.g., trialkylamine methacrylimide, and dimethyl-(2-hydroxypropyl)amine methacrylimide); mono-olefinic sulfonic acids and their salts, (such as sodium ethylene sulfonate, sodium styrene sulfonate and 2-acrylamideo-2-methylpropanesulfonic acid)). Other polymer include those prepared from the following monomers containing nitrogen in the non-cyclic or cyclic backbone of the monomer: 1-vinyl-imidazole, 1-vinyl-indole, 2-vinyl imidazole, 4(5)-vinyl-imidazole, 2-vinyl-l-methyl-imidazole, 5-vinyl-pyrazoline, 3-methyl-5-isopropenyl-pyrazole, 5-methylene-hydantoin, 3-vinyl-2-oxazolidone, 3-methacrylyl-2-oxazolidone, 3-methacrylyl-5-methyl-2-oxazolidone, 3-vinyl-5-methyl-2-oxazolidone, 2- and 4-vinyl-pyridine, 5-vinyl-2-methyl-pyridine, 2-vinyl-pyridine-l-oxide, 3-isopropenyl-pyridine, 2- and 4-vinyl-piperidine, 2- and 4-vinyl-quinoline, 2,4-dimethyl-6-vinyl-s-triazine, and 4-acrylyl-morpholine.

For certain embodiments, the microparticles are prepared from amine-containing organic polymers. Preferably, the amine-containing hydrophilic polymer include a quaternary amine, and more preferably, the amine-containing polymer is a quaternary ammonium salt of an organic polymer. Examples include, but are not limited to, polymerization products of cationic vinyl monomers as disclosed in EP 0 489 967 A1, and inherently antimicrobial quaternary amine polymers as described in U.S. Pat. No. 6,039,940.

For certain embodiments, the microparticles are prepared from carboxylic acid-containing organic polymers. Examples of such microparticles include sodium polyacrylate (i.e., a copolymer of sodium acrylate and acrylic acid) microparticles such as those commercially available under the trade designation SALCARE SC91 from Ciba Specialty Chemicals (High Point, NC).

Preferred microparticles are described in EP 172 724 A2 and EP 126 528 A2 made by reverse phase polymerization and have a dry particle size below 4 microns.

Other suitable polymeric microparticles can be prepared from a quaternary ammonium monomer, which is a salt having an organo-ammonium group and a monoethylenically unsaturated group. For certain embodiments, the quaternary ammonium monomer has the following general Formula (I):



Formula (I)

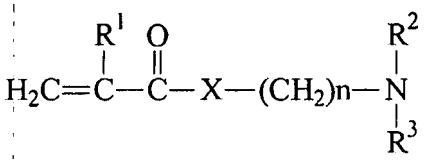
wherein: n is 2 to 10, preferably 2 to 3; R^1 is H or CH_3; R^2, R^3, and R^4 are each independently linear or branched organic groups, preferably having 1 to 16 carbon atoms (on average); X is O or NH; and Y^- is an acceptable anionic counterion to the N^+ of the quaternary ammonium group (e.g., one that does not adversely affect the polymerization of the monomers or antimicrobial activity of an added antimicrobial agent).

Preferably, R^2, R^3, and R^4 are each independently alkyl, aryl, alkaryl, or aralkyl groups. Alkyl groups are preferably lower alkyl, having 1 to 16 carbon atoms (on average) with methyl and ethyl groups being particularly preferred. Aryl is preferably phenyl but can be any suitable aromatic moiety such as those selected from the group consisting of phenyl, thiophenyl, naphthyl, biphenyl, pyridyl, pyrimidinyl, pyrazyl, pyridazinyl, furyl, thienyl, pyrryl, quinolinyl, bipyridyl, and the like. Representative of an aralkyl grouping is benzyl and representative of an alkaryl grouping is tolyl. X is preferably O. Representative counterions (Y^-) are Cl^-, Br^-, HSO_4^-, $CH_3CH_2OSO_3^-$, and $CH_3OSO_3^-$, with the chloride salts being particularly preferred. Alkyl groups can be straight or branched chain and alkyl and aryl groups can be substituted by non-interfering substituents that do not obstruct with the functionality of the polymers.

Useful copolymerizable quaternary ammonium monomers include, but are not limited to, those selected from 2-(meth)acryloxyethyl trialkyl ammonium halides and sulfates, and mixtures thereof. Examples of such compounds include, but are not limited to, 2-(meth)acryloxyethyl trimethyl ammonium chloride, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_3Cl$; 2-(meth)acryloxyethyl trimethyl ammonium methyl sulfate, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_3OSO_2OCH_3$; 2-(meth)acryloxyethyl methyl diethyl ammonium methyl sulfate, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)(C_2H_5)_2OSO_2OCH_3$; 2-(meth)acryloxyethyl dimethyl benzyl ammonium chloride, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_2(C_6H_5CH_2)Cl$ (all of the

preceding monomers available from Ciba Specialty Chemicals, Woodbridge, NJ); 2-(methylacryloxy)ethyl dimethyl hexadecyl ammonium bromide, $CH_2=C(CH_3)CO_2CH_2CH_2N(CH_3)_2(C_{16}H_{33})Br$ (described in U.S. Pat. No. 5,437,932 (Ali et al.)); and the like. Various combinations of these monomers can be used if desired. Due to their availability, effectiveness in reinforcing (meth)acrylate polymers and their antimicrobial activity, particularly preferred quaternary ammonium monomers are 2-acryloxyethyl trimethyl ammonium methyl sulfate and 2-acryloxyethyl methyl diethyl ammonium methyl sulfate. Such monomers are typically hydrophilic. Various combinations of other monoethylenically unsaturated monomers that are reinforcing monomers can be used in the polymers of the present invention. Such reinforcing monomers include, but are not limited to, acrylic acid, methacrylic acid, ethylene vinyl acetate, and N,N-dimethylacrylamide.

As an alternative approach to providing polymers that contain a quaternary ammonium functional unit, it is possible to start with an amine monomer and form the quaternary ammonium unit following polymerization. For certain embodiments, the amine monomers have the following general Formula (II):



Formula (II)

wherein n, R^1, R^2, R^3, and X are the same as defined for Formula (I).

As stated above, the microparticles can be in an emulsion, such as an inverse emulsion. One type of inverse emulsion can be defined as a continuous hydrophobic liquid phase (e.g., mineral oil) and hydrophilic polymer particles dispersed within the hydrophobic liquid phase. Suitable examples of such materials are described in EP 0 126 528 A2. Such a material is commercially available under the trade designation SALCARE from Ciba Specialty Chemicals (High Point, NC). Suitable examples include SALCARE 95 and 96 which include a cationic homopolymer of the methyl chloride quaternary salt of 2-(dimethylamino)ethyl methacrylate (CAS No. 26161-33-1).

Other amine-containing polymers can be made from amine-containing monomers as described below and in EP 0 489 967 A1 and U.S. Pat. No. 6,039,940.

Monomers can be polymerized using techniques such as solution polymerization, emulsion polymerization, bulk polymerization, suspension polymerization, and the like. In particular, emulsion polymerization and suspension polymerization are preferable because the molecular weight of the polymer becomes high; solution polymerization is preferable because the molecular weight distribution is comparatively narrow; and bulk polymerization is favorable because no solvent is used.

In such polymerizations, initiators can be used to generate free-radicals upon the application of activating energy such as those conventionally used in the polymerization of ethylenically unsaturated monomers. Included among useful free-radical initiators are the thermally activated initiators such as organic peroxides, organic hydroperoxides, and azo-compounds. Representative examples of such initiators include, but are not limited to, benzoyl peroxide, tertiary-butyl perbenzoate, diisopropyl peroxydicarbonate, cumene hydroperoxide, azobis(isobutyronitrile), and the like. Generally, the thermal initiators are typically used in amounts from 0.01 to 5 percent by weight of monomer.

The polymerization of the polymer may also be initiated by photoinitiators. Such photochemically activated initiators are well known and have been described in the polymerization art; e.g., Chapter II of "Photochemistry" by Calvert and Pitts, John Wiley and Sons (1966) and in *Progress in Organic Coatings*, *13*, 123-150 (1985). Representative examples of such initiators include benzoin, benzoin methyl ether, benzoin isopropyl ether, benzoin isobutyl ether, and 2-hydroxy-2-methyl-1-phenyl-1-propane, benzildimethylketal and benzildiethylketal, 2-hydroxy-1-(4-(2-hydroxyethoxy)phenyl)-2-methyl-1-propanone. A presently preferred photoinitiator is 2-hydroxy-1-(4-(2-hydroxyethoxy)phenyl)-2-methyl-1-propanone. Generally, photoinitiators are used in amounts from 0.01 to 5 percent by weight of monomer.

The polymerization of the polymer may also be initiated by electromagnetic radiation such as electron beams and the gamma-rays of cobalt 60, and the like. The irradiation dose is typically between 1 and 100 kGy.

The polymer may be crosslinked by adding a crosslinking compound or through electron beam or gamma radiation. A crosslinking compound can be a multi-ethylenically unsaturated compound wherein the ethylenic groups are vinyl groups,

allyl groups, and/or methallyl groups bonded to nitrogen or oxygen atoms. Exemplary compounds include divinyl, diallyl or dimethallyl esters (e.g., divinyl succinate, divinyl adipate, divinyl maleate, divinyl oxalate, divinyl malonate, divinyl glutarate, diallyl itaconate, diallyl maleate, diallyl fumarate, diallyl diglycolate, diallyl oxalate, diallyl adipate, diallyl succinate, diallyl azelate, diallyl malonate, diallyl glutarate, dimethallyl maleate, dimethallyl oxalate, dimethallyl malonate, dimethallyl succinate, dimethallyl glutarate, and dimethallyl adipate), divinyl, diallyl or dimethallyl ethers (e.g., diethyleneglycol divinyl ether, butanediol divinyl ether, ethylene glycol divinyl ether, ethylene glycol diallyl ether, diethylene glycol diallyl ether, butane diol diallyl ether, ethylene glycol dimethallyl ether, diethylene glycol dimethallyl ether, and butane diol dimethallyl ether), divinyl, diallyl or dimethallyl amides including bis(N-vinyl lactams), (e.g., 3,3'-ethylidene bis(N-vinyl-2-pyrrolidone)), and divinyl, diallyl or dimethallyl ureas.

OPTIONAL PLASTICIZING AGENTS

Plasticizing agents (i.e., plasticizers) selected for use in the compositions of the present invention can possess a range of properties. Generally, the plasticizing agents can be liquid, semi-solid or solid, have a range of molecular weights and architectures (e.g., be monomeric or polymeric in nature), and are compatible with the other components of the polymer composition. Additionally, mixtures of solid and liquid, monomeric and polymeric and other combinations of plasticizing agents can be used in the present invention.

For certain embodiments, elastomeric plasticizing agents can be used. Such plasticizing agents can be derived from low molecular weight naphthalenic oils, or low molecular weight acids, or alcohols, which are then esterified with respectively a monofunctional alcohol or monofunctional acid. Examples of these are mineral oil, cetostearyl alcohol, cetyl alcohol, cholesterol, coconut oil, oleyl alcohol, steryl alcohol, and squalane. Some elastomers are more compatible with esters of mono- and multibasic acids, such as isopropyl myristate, isopropyl palmitate, dibutyl phthalate, diisoctyl phthalate, dibutyl adipate, dibutyl sebacate, and the like. Useful polymeric plasticizing agents include non-acrylic plasticizing agents, which are typically derived from cationically or free-radically polymerizable monomers, condensation polymerizable monomers, or ring-opening polymerizable monomers to make low

molecular weight polymers. Examples of these polymeric plasticizing agents include materials such as polyurethanes, polyureas, polyvinylethers, polyethers, polyesters, and the like.

Useful plasticizing agents are compatible with the polymer(s) of the hydrophobic polymer matrix, such that once the plasticizing agent is mixed with therein, the plasticizing agent does not phase separate from the hydrophobic polymer matrix. By "phase separation" or "phase separate", it is meant that by differential scanning calorimetry (DSC) no detectable thermal transition, such as a melting or glass transition temperature can be found for the pure plasticizing agent in the plasticized composition. Some migration of the plasticizing agent from or throughout the plasticized composition can be tolerated, such as minor separation due to composition equilibrium or temperature influences, but the plasticizing agent does not migrate to the extent of phase separation between the polymer(s) of the hydrophobic polymer matrix and the plasticizing agent.

Preferably, useful plasticizing agents are non-reactive, thus preventing copolymerization with the reactive groups of the polymers in the hydrophobic polymer matrix of the hydrophilic microparticles. Thus, for example, plasticizing agents having acrylate functionality, methacrylate functionality, styrene functionality, or other ethylenically unsaturated, free radically reactive functional groups are generally not used.

Generally, liquid plasticizing agents are readily compoundable with hydrophobic polymer matrix that includes one or more elastomers using an extruder. In addition, liquid plasticizing agents may be delivered directly to a tacky elastomer, if used in the composition, in order to make it less tacky or non-tacky.

Although somewhat more challenging to use, semi-solid (such as petrolatum) and solid plasticizing agents (such as paraffin wax, beeswax, microcrystalline wax, cetyl esters wax) can advantageously be used in compositions of the present invention where the controlled plasticization is desired. For example, hot melt processible compositions can be easily transported and handled prior to melt compounding if the hydrophobic polymer matrix and the plasticizing agent components are solid and non-tacky. Once heated to the melting or glass transition temperature of the solid plasticizing agent, the polymer of the matrix is plasticized.

The plasticizing agent is typically used in amounts of from about 1 to 2000 parts by weight per 100 parts of the hydrophobic polymer.

OPTIONAL BIOACTIVE AGENTS

The polymer compositions of the present invention can optionally include a bioactive agent. Typically, the bioactive agents are antimicrobial (e.g., antibacterial or antifungal) agents. Such actives are capable of destroying microbes, preventing the development of microbes or preventing the pathogenic action of microbes. An effective amount of a bioactive agent may be added to the present compositions. If use, this amount is typically at least 0.001%, based on the total weight of the composition.

Examples include, but are not limited to, beta-lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, 2,4,4'-trichloro-2'-hydroxy diphenyl ether, phenoxyethanol, phenoxy propanol, phenoxyisopropanol, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, hexamidine isethionate, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole, tetracycline hydrochloride, erythromycin, zinc erythromycin, erythromycin estolate, erythromycin stearate, amikacin sulfate, doxycycline hydrochloride, capreomycin sulfate, chlorhexidine gluconate, chlorhexidine hydrochloride, chlortetracycline hydrochloride, oxytetracycline hydrochloride, clindamycin hydrochloride, ethambutol hydrochloride, metronidazole hydrochloride, pentamidine hydrochloride, gentamicin sulfate, kanamycin sulfate, lineomycin hydrochloride, methacycline hydrochloride, methenamine hippurate, methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, miconazole, ketaconazole, amanfadine hydrochloride, amanfadine sulfate, octopirox, parachlorometa xylenol, nystatin, tolnaftate, pyrithiones (especially zinc pyrithione which is also known as ZPT), dimethyldimethylol hydantoin, methylchloroisothiazolinone/methylisothiazolinone, sodium sulfite, sodium bisulfite, imidazolidinyl urea, diazolidinyl urea, benzyl alcohol, 2-bromo-2-nitropropane-1,3-diol, formalin (formaldehyde), iodopropenyl butylcarbamate, chloroacetamide, methanamine, methyldibromonitrile glutaronitrile (1,2-dibromo-2,4-dicyanobutane), glutaraldehyde, 5-bromo-5-nitro- 1,3-dioxane,

phenethyl alcohol, o-phenylphenol/sodium o-phenylphenol, sodium hydroxymethylglycinate, polymethoxy bicyclic oxazolidine, dimethoxane, thimersal dichlorobenzyl alcohol, captan, chlorphenenesin, dichlorophene, chlorobutanol, glyceryl laurate, halogenated diphenyl ethers like 2,4,4'-trichloro-2'-hydroxy-diphenyl ether, 2,2'-dihydroxy-5,5'-dibromo-diphenyl ether, phenolic compounds like phenol, 2-methyl phenol, 3-methyl phenol, 4-methyl phenol, 4-ethyl phenol, 2,4-dimethyl phenol, 2,5-dimethyl phenol, 3,4-dimethyl phenol, 2,6-dimethyl phenol, 4-n-propyl phenol, 4-n-butyl phenol, 4-n-amyl phenol, 4-tert-amyl phenol, 4-n-hexyl phenol, 4-n-heptyl phenol, mono- and poly-alkyl and aromatic halophenols such as p-chlorophenol, methyl p-chlorophenol, ethyl p-chlorophenol, n-propyl p-chlorophenol, n-butyl p-chlorophenol, n-amyl p-chlorophenol, sec-amyl pchlorophenol, n-hexyl p-chlorophenol, cyclohexyl p-chlorophenol, n-heptyl p-chlorophenol, n-octyl p-chlorophenol, o-chlorophenol, methyl o-chlorophenol, ethyl o-chlorophenol, n-propyl ochlorophenol, n-butyl o-chlorophenol, n-amyl o-chlorophenol, tert-amyl o-chlorophenol, n-hexyl o-chlorophenol, n-heptyl o-chlorophenol, o-benzyl p-chlorophenol, o-benzyl-m-methyl p-chlorophenol, o-benzyl-m, m-dimethyl p-chlorophenol, o-phenylethyl p-chlorophenol, o-phenylethyl-m-methyl p-chlorophenol, 3-methyl p-chlorophenol, 3,5-dimethyl p-chlorophenol, 6-ethyl-3-methyl p-chlorophenol, 6-n-propyl-3-methyl p-chlorophenol, 6-iso-propyl-3-methyl p-chlorophenol, 2-ethyl-3,5-dimethyl p-chlorophenol, 6-sec-butyl-3-methyl p-chlorophenol, 2-iso-propyl-3,5-dimethyl pchlorophenol, 6-diethylmethyl-3-methyl p-chlorophenol, 6-iso-propyl-2-ethyl-3-methyl p-chlorophenol, 2-sec-amyl-3,5-dimethyl p-chlorophenol 2-diethylmethyl-3,5-dimethyl p-chlorophenol, 6-sec-octyl-3-methyl p-chlorophenol, p-chloro-m-cresol, p-bromophenol, methyl pbromophenol, ethyl p-bromophenol, n-propyl p-bromophenol, n-butyl p-bromophenol, n-amyl p-bromophenol, sec-amyl p-bromophenol, n-hexyl p-bromophenol, cyclohexyl p-bromophenol, o-bromophenol, tert-amyl o-bromophenol, n-hexyl o-bromophenol, n-propyl-m,m-dimethyl o-bromophenol, 2-phenyl phenol, 4-chloro-2-methyl phenol, 4-chloro-3-methyl phenol, 4-chloro-3,5-dimethyl phenol, 2,4-dichloro-3,5-dimethylphenol, 3,4,5,6-terabromo-2-methylphenol, 5-methyl-2-pentylphenol, 4-isopropyl-3-methylphenol, para-chloro-meta-xylenol (PCMX), chlorothymol, 5-chloro-2-hydroxydiphenylmethane, resorcinol and its derivatives including methyl resorcinol, ethyl resorcinol, n-propyl resorcinol, n-butyl resorcinol, n-amyl resorcinol, n-hexyl

resorcinol, n-heptyl resorcinol, n-octyl resorcinol, n-nonyl resorcinol, phenyl resorcinol, benyl resorcinol, phenylethyl resorcinol, phenylpropyl resorcinol, p-chlorobenzyl resorcinol, 5-chloro 2,4-dihydroxydiphenyl methane, 4'-chloro 2,4-dihydroxydiphenyl methane, 5-bromo 2,4-dihydroxydiphenyl methane, and 4'-bromo 2,4-dihydroxydiphenyl methane, bisphenolic compounds like 2,2'-methylene bis (4-chlorophenol), 2,2'-methylene bis (3,4,6-trichlorophenol), 2,2'-methylene bis (4-chloro-6-bromophenol), bis (2-hydroxy-3,5-dichlorophenyl) sulphide, and bis (2-hydroxy-5-chlorobenzyl)sulphide, benzoic esters (parabens) like methylparaben, propylparaben, butylparaben, ethylparaben, isopropylparaben, isobutylparaben, benzylparaben, sodium methylparaben, and sodium propylparaben, halogenated carbanilides (e.g., 3,4,4'-trichlorocarbanilides), 3-trifluoromethyl-4,4'-dichlorocarbanilide, 3,3',4-trichlorocarbanilide, etc.), cationic actives such as benzalkonium chloride, and clotrimazole.

Another class of antimicrobial agents (i.e., actives), which are useful in the present invention, are the so-called "natural" antibacterial actives, referred to as natural essential oils. These actives derive their names from their natural occurrence in plants. Typical natural essential oil antibacterial actives include oils of anise, lemon, orange, rosemary, wintergreen, thyme, lavender, cloves, hops, tea tree, citronella, wheat, barley, lemongrass, grapefruit seed, cedar leaf, cedarwood, cinnamon, fleagrass, geranium, sandalwood, violet, cranberry, eucalyptus, vervain, peppermint, gum benzoin, basil, fennel, fir, balsam, menthol, ocmea origanum, Hydastis carradensis, Berberidaceae daceae, Ratanhiae and Curcuma longa. Also included in this class of natural essential oils are the key chemical components of the plant oils, which have been found to provide the antimicrobial benefit. These chemicals include, but are not limited to, anethol, catechole, camphene, thymol, eugenol, eucalyptol, ferulic acid, farnesol, hinokitiol, tropolone, limonene, menthol, methyl salicylate, carvacol, terpineol, verbenone, berberine, ratanhiae extract, caryophellene oxide, citronellic acid, curcumin, nerolidol and geraniol.

The bioactive agent can be present in the polymer composition in an amount to produce a desired effect (e.g., antimicrobial effect).

OTHER OPTIONAL ADDITIVES

The polymer compositions of the present invention can include a wide variety of optional additives. Examples include, but are not limited to, secondary bioactive agents, swelling agents, fillers, pigments, dyes, tackifiers, crosslinking agents, stabilizers, compatibilizers, extruding aids, chain transfer agents, and combinations thereof.

In certain embodiments, polymer compositions of the present invention can include fillers, which can be inorganic or organic. Examples of inorganic fillers include, but are not limited to, barytes, chalk, gypsum, kieserite, sodium carbonate, titanium dioxide, cerium oxide, silica dioxide, kaolin, carbon black, and hollow glass microbeads. Examples of organic fillers include, but are not limited to, powders based on polystyrene, polyvinyl chloride, urea-formaldehyde, and polyethylene. The fillers may be in the form of fibers, such as chopped fibers. Examples of suitable chopped fibers include glass fibers (typically 0.1 millimeter (mm) to 1 mm long) or fibers of organic origin such as, for example, polyester or polyamide fibers.

In order to confer color to the polymer compositions it is possible to use dyes or colored pigments of an organic or inorganic basis such as, for example, iron oxide or chromium oxide pigments or phthalocyanine- or monoazo-based pigments.

METHODS OF PREPARATION OF POLYMER COMPOSITIONS AND ARTICLES

For certain embodiments, the components are combined in a manner to produce a polymer composition wherein at least a portion of the bioactive agent, if used, is incorporated within microparticles. Preferably, this results from combining the components by hot mixing without a solvent (so-called hot-melt process), by blending an elastomer with an oily plasticizer and antioxidants, and then by adding a hydrocolloid either as finely divided powder or as an inverse emulsion. If active agents are provided, these may be added to either the elastomer or the hydrocolloid.

In certain embodiments, an inverse emulsion that includes hydrophilic organic microparticles is combined with water and a bioactive agent under conditions effective to distribute (preferably, dissolve) at least a portion of the bioactive agent in the hydrophilic organic microparticles. Optionally, a secondary organic polymer can be added to the mixture of the inverse emulsion, solvent, and an optional bioactive agent.

Once sufficiently mixed to impregnate at least a portion of the bioactive agent, if used, into the hydrophilic particles, the solvent is removed, if desired.

In other embodiments, monomers for a hydrophilic organic polymer are combined with an optional bioactive agent under conditions effective to polymerize the monomers and distribute (preferably dissolve) at least a portion of the bioactive agent, if used, in the hydrophilic organic polymer. The bioactive agent, if used, can be present during the polymerization process or added after the polymerization is complete. Optionally, a secondary organic polymer can be added to the hydrophilic organic polymer with the bioactive agent, if used, distributed therein.

The polymer compositions, with or without the bioactive agent therein, can be melt processed (e.g., extruded or molded) or solvent cast to form the desired products (e.g., wound dressing).

The materials used to prepare the polymer compositions of the present invention are melt processable if they are fluid or pumpable, and they do not significantly degrade or gel at the temperatures used to melt process (e.g., extruding or compounding) the composition (e.g., at least 50°C and up to 300°C). Preferably, such materials have a melt viscosity of at least 10 poise and often up to 1,000,000 poise, as measured by capillary melt rheometry at the processing temperatures and shear rates employed in extrusion. Typically, suitable materials possess a melt viscosity within this range at a temperature of at least 175°C and often up to 225°C and a shear rate of 100 seconds^{-1}.

Continuous melt process forming methods include drawing the extruded composition out of a film die and subsequently contacting a moving plastic web or other suitable backing. Another continuous forming method involves directly contacting the extruded composition to a rapidly moving plastic web or other suitable substrate. In this method, the extruded composition can be applied to a moving web using a die having flexible die lips such a reverse orifice coating die and other contact dies using rotating rods. The composition can also be extruded in the form of continuous fibers and blown micro-fiber webs as disclosed in Wente, Van A., "Superfine Thermoplastic Fibers," Industrial Engineering Chemistry, Vol. 48, pp. 1342-1346; Wente, Van A. et al., "Manufacture of Superfine Organic Fibers," Report No. 4364 of the Naval Research Laboratories, published May 25, 1954; and U.S. Pat. Nos. 5,176,952 and 3,841,953. After melt process forming the composition is solidified by

quenching using either direct methods, such as chill rolls or water baths, or indirect methods, such as air or gas impingement, or both.

Articles can be prepared using compositions described herein according to a variety of methods, particularly coating methods. When a porous substrate is coated, the process of coating the porous substrate with the composition typically allows the yarns, filaments, or film to be properly trapped in the composition, while leaving most of the apertures unobstructed by the composition. Depending on the structure of the support used, the amount of composition employed will vary over a wide range (typically from 50 grams per square meter (g/m^2) to 300 g/m^2, and preferably from 60 g/m^2 to 160 g/m^2).

In certain embodiments, the coating can be carried out hot, without a solvent, using a continuous process in which the substrate is directed over a first coating roll covered with a layer of molten composition having a predetermined thickness, and then over a second roll which removes the composition lying within the apertures of the substrate. The substrate thus covered with gel only on the yarns, filaments, or film is then cooled in a stream of air so that the composition cannot flow and remains uniformly distributed around the yarns, filaments, or film. If necessary, a system producing a laminar stream of air is provided, which system is able both to correct the distribution of the composition around the yarns, filaments, or film and to unblock any substrate apertures, which would not have been open in the previous step of the process.

According to a variant of this process, a substrate can be passed through a bath of molten polymeric composition (for example, at a temperature of 120°C to 200°C). The substrate covered with molten composition is then passed between two fixed rolls pressed against each other with a predetermined gap, so as to remove the excess composition. The amount of composition remaining on the yarns, filaments, or film depends essentially on the gap set between the fixed rolls. The covered product is then cooled and treated in a manner similar to the previous process.

If desired, the cooled coated substrate can be covered with two protective films (for example, thin polyester films). These films may or may not require a nonstick treatment and can function to facilitate extraction from a package and in handling the article. If desired, the coated substrate can be cut into individual compresses, of sizes suitable for the use, packaged in sealed sachets, and sterilized.

Solvent casting may also be used to prepare the articles of the present invention. This method typically employs a common solvent, selected for compatibility with the polymer composition components. Such common solvents include, for example, toluene and tetrahydrofuran. Specific selection of a common solvent for a particular subset of the present invention is within the skill of the art. In the solvent casting method, the materials included in the composition are blended to form a uniform mixture, then coated onto a carrier web or a backing (described below) using a known coating technique such as curtain coating, die coating, knife coating, roll coating, or spray coating. A preferred coating method is knife coating. The solvent is then removed from the coated backing, usually with the aid of a drying oven for a time and temperature selected to remove any undesirable level of residual solvent.

Layered constructions can also be prepared using lamination, coating, or extrusion techniques known to one of skill in the art and as described, for example, in U.S. Pat. No. 6,379,791.

If desired, compositions of the present invention can be sterilized. Methods of sterilization include treatment with electron beam or gamma radiation.

WOUND DRESSINGS

The polymer compositions of the present invention can be used in wound dressings, i.e., medical articles that are applied directly to or contact a wound. Such articles include a backing (i.e., a support substrate) that is porous. The composition of the present invention can be coated on the support substrate or impregnated into it, for example.

Suitable materials are preferably flexible, and may be fabric, non-woven or woven polymeric films, metallic, paper, and/or combinations thereof. More specifically, it is desirable to use a liquid permeable (e.g., with respect to moisture vapor), open apertured substrate (e.g., a scrim). For certain embodiments it is desirable to use an open- or closed-cell foam, such as that disclosed in U.S. Pat. Nos. 6,548,727 and 5,409,472.

The substrates (i.e., backings) are preferably porous to allow the passage of wound fluids, moisture vapor, and air. Hence, the porous substrates are liquid permeable.

Suitable porous substrates include knits, wovens (e.g., cheese cloth and gauze), nonwovens (including spun-bonded nonwovens), extruded porous sheets, and perforated sheets. The apertures (i.e., openings) in the porous substrates are of sufficient size and sufficient number to facilitate high breathability. For certain embodiments, the porous substrates have at least 1 aperture per square centimeter. For certain embodiments, the porous substrates have no greater than 225 apertures per square centimeter. For certain embodiments, the apertures have an average opening size (i.e., the largest dimension of the opening) of at least 0.1 millimeter (mm). For certain embodiments, the apertures have an average opening size (i.e., the largest dimension of the opening) of no greater than 0.5 cm.

For certain embodiments, the porous substrates have a basis weight of at least 5 grams/meter^2. For certain embodiments, the porous substrates have a basis weight of no greater than 200 grams/meter^2.

The porous substrates (i.e., backings) are preferably flexible yet resistant to tearing. For certain embodiments, the thickness of the porous substrates is at least 0.0125 mm. For certain embodiments, the thickness of the porous substrates is no greater than 3 mm.

The porous substrates may be opaque or translucent. Normally they have a skin color, but "designer" colors and patterns, as well as cartoon character designs, are becoming popular.

Materials of the backing or support substrate include a wide variety of materials including paper, natural or synthetic fibers, threads and yarns made from materials such as cotton, rayon, wool, hemp, jute, nylon, polyesters, polyacetates, polyacrylics, alginates, ethylene-propylene-diene rubbers, natural rubber, polyesters, polyisobutylenes, polyolefins (e.g., polypropylene polyethylene, ethylene propylene copolymers, and ethylene butylene copolymers), polyurethanes (including polyurethane foams), vinyls including polyvinylchloride and ethylene-vinyl acetate, polyamides, polystyrenes, fiberglass, ceramic fibers, and/or combinations thereof.

For particular purposes, the backing may be coated on one or both major surfaces, with a primer or a release agent, which may be a low-adhesion backsize (LAB) material. For example, when using a plasticized polyvinylchloride (PVC) backing, an embodiment of the present invention comprising a butadiene- or isoprene-containing polymer along with a polyisoprene-polyvinylpyridine (PI-PVP)

compatibilizer has a particular advantage in that the composite PSA has an affinity for acidic PVC.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Materials

KRATON D1124K- radial 4-arm star polystyrene-polyisoprene $(SI)_4$ thermoplastic elastomeric copolymer having 30 wt-% polystyrene, available from KRATON Polymers, Houston, Texas.

SALCARE SC95- sub-micron cationic inverse emulsion consisting of polymerized methylchloride quaternary ammonium salt of dimethylaminoethylmethacrylate (DMAEMA) microparticles dispersed in mineral oil and proprietary non-ionic surfactant, available from Ciba Specialty Chemicals, High Point, North Carolina.

SALCARE SC91 -sub-micron anionic inverse emulsion consisting of polymerized sodium acrylate copolymer microparticles dispersed in mineral oil and proprietary non-ionic surfactant, available from Ciba Specialty Chemicals, High Point, North Carolina.

KAYDOL -mineral oil available from Crompton Corporation, formerly Witco Corporation.

IRGANOX 1010 -Phenolic antioxidant available from Ciba Specialty Chemicals, Tarrytown, New York.

Polyester Knitted Fabric was a 24 mesh polyester knit (61 g/m^2) purchased from Lamports Filter Media, Inc, Cleveland, OH.

Peel Adhesion Test

Peel adhesion is measured as 180° peel from steel plates, at 23°C, 50% relative humidity (RH), 305 millimeters per minute (mm/min), 25 mm wide using a Model 3M90 Slip/Peel tester (IMASS, Inc., Accord, MA). The samples were conditioned for 24 hours at controlled temperature and humidity. After conditioning the samples were

adhered to a stainless steel panel using 2 kilograms (kg) roller and 4 passes. The samples were peeled from the stainless steel plate after 15 minutes of dwell time using a 0.305 meter/minute (m/min) peel rate. Typically, two 0.13 meter (m) long samples were measured and the average peel force recorded in ounces/inch (oz/in) and converted to Newtons per decimeter (N/dm).

Saline Absorbency Test

Samples (2.54 cm by 2.54 cm) were soaked in saline. The samples were removed from the saline at various times and were lightly dabbed with a paper towel. The weight was recorded and the samples were placed back into the saline solution. The weight of saline absorbed per weight of dry coating was calculated as a function of swelling time in the saline using the following equation: (weight saline absorbed)/(dry coating sample weight) = [(saline swollen weight) – (dry sample weight)]/[(dry sample weight) – (weight of substrate)].

Preparation of Examples

Examples were prepared by first preparing a hydrophobic gel and then incorporating hydrophilic microparticles and a support substrate to make an article.

Preparation of Gel

KRATON D1124K styrene-isoprene-styrene (SIS) pellets were gravimetrically fed into the feed throat (barrel section 1) of a Werner Pfleiderer ZSK30 co-rotating twin-screw extruder (TSE) having a 30 mm diameter and 15 barrel sections.

Each temperature zone was a combination of two barrel sections (e.g., Zone 1 corresponded to barrel sections 2 and 3). Barrel section 1 was controlled at full cooling capacity for all SIS gel lots. A powdered antioxidant (IRGANOX 1010) was also gravimetrically fed into barrel section 1. KAYDOL mineral oil was heated and added to the TSE as described in International Publication No. WO 97/00163. The disclosed compounding process provides a method for making a gel by melting of the SIS elastomer followed by addition of the heated mineral oil. Heated mineral oil was sequentially injected into barrel sections 4, 6, 8, 10 and 12, respectively. The TSE screw speed was controlled to 400 revolutions per minute (rpm). The TSE temperature profile was controlled to 204°C, 227°C, 227°C, 204°C, 182°C, 171°C, and 93°C for

zones 1-7, respectively. The heated oil injections were controlled to 204°C, 204°C, 204°C, 177°C, and 177°C, respectively. Table 1 contains the material flow rates and Table 2 contains the compositional information for the SIS gel.

Table 1. SIS gel lot flow rates

SIS (g/min)	Barrel Section(S) and Oil addition number and Rate (g/min)					Total KAYDOL Oil (g/min)	IRGANOX 1010 (g/min)	Total Flow Rate (g/min)
	S4 Oil 1	S6 Oil 2	S8 Oil 3	S10 Oil 4	S12 Oil 5			
227	74	100	120	120	108	522	8	757

Table 2. SIS gel composition

SIS Type	SIS (wt-%)	KAYDOL oil (wt-%)	IRGANOX 1010 (wt-%)
KRATON D1124K	30.0	69.0	1.0

Preparation of Dressing

Examples 1 and 2 were prepared by combining the pre-compounded SIS gel with SALCARE SC95 or SALCARE SC91 in a Haake 25 mm diameter, fully intermeshing counter-rotating TSE. Examples 1 and 2 were prepared by re-melting the SIS gel in a Bonnot extruder operating at 127°C. The molten gel was injected at 22.8 grams per minute into barrel section 2 of the TSE. SALCARE inverse emulsion was injected at ambient temperature into barrel section 4 at 15.2 grams per minute (g/min) using a Zenith gear pump. The TSE was controlled at 300 rpm screw speed and 121°C temperature. The total material throughput was 38.0 grams per minute. The SIS gel/SALCARE blend was discharged out of the TSE into a transport hose using a Zenith gear pump. A transport hose conveyed the molten gel blend to a 0.15meter (m) wide single orifice film die. The transport hose and die were both controlled to 121°C.

The molten gel blend was extruded into a nip formed by two gapped and polished steel rolls controlled to 110°C. A polyester (PET) knitted fabric having 0.8 mm by 0.7 mm (0.56 mm^2) rectangular open apertures, 0.20 millimeter (mm) thickness and 0.15 meter (m) width was also fed into the nip at 1.4 m/min speed. As the fabric exited the nip, the gel-coated article was cooled in air before being wound up with an inserted paper release liner. After air-cooling to ambient temperature a coated fabric having 0.75 mm by 0.6 mm (0.45 mm^2) rectangular open apertures was obtained. Table 3 contains the process conditions and Table 4 contains the compositional information for Examples 1-2.

Table 3. Examples 1-2 process conditions

Ex.	SIS Gel Input (barrel section number)	SALCARE Input (barrel section number)	Steel Roll Gap (mm)	Coating Speed (m/min)	Coating Weight (g/m^2)
1	2	4	0.37	2.1	147
2	2	4	0.25	2.1	78

Table 4. Examples 1-2 compositions

Ex.	SIS (wt-%)	IRGANOX 1010 (wt-%)	SALCARE Type	SALCARE (wt-%)	KAYDOL oil (wt-%)
1	18.0	0.6	SC95	40.0	41.4
2	18.0	0.6	SC91	40.0	41.4

Adhesion and Asorbency of Examples

The gel coated PET fabrics (Examples 1-2) and 1 mm thick slabs having the compositions of Example 2 were tested for 180° peel adhesion from stainless steel using the peel test method described. The 180° peel adhesion from stainless steel was 0.1 N/dm for the gel slab (Example 2) and 0.0 N/dm for the gel coated fabric samples (Examples 1 and 2). The extremely low 180° peel adhesion demonstrates the inability of the composition and articles of the invention to form a strong adhesive bond.

Consequently, the composition and articles of the invention are considered non-adherent or non-adhesive.

Examples 1-2 were tested for their ability to absorb 0.8 wt-% NaCl (saline). Samples (2.54 cm by 2.54 cm) of Examples 1 and 2 were soaked in saline. Absorbency was measured by the Saline Absorbency test as a function of time with the results in Table 6.

Table 6. Saline absorbency vs. time for Examples 1-2

Ex.	SIS (wt-%)	SALCARE Type	0.5 hour Saline Absorb.	1 hour Saline Absorb.	2 hours Saline Absorb.
1	18.0	SC95	1.9	2.2	2.6
2	18.0	SC91	3.6	4.2	4.8

The saline absorbency data demonstrates that the composition and article of the invention can absorb an amount of saline that is 1-5 times their dry weight. All samples remained intact after saline exposure.

WHAT IS CLAIMED IS:

1. A wound dressing comprising an apertured liquid permeable substrate and an absorbent, nonadherent polymer composition comprising:

a hydrophobic organic polymer matrix;

an optional plasticizing agent; and

hydrophilic organic microparticles.

2. The wound dressing of claim 1 wherein the hydrophobic organic polymer matrix comprises a styrene-isoprene-styrene copolymer, a styrene-butadiene-styrene copolymer, or mixtures thereof.

3. The wound dressing of claim 1 wherein the composition comprises a plasticizing agent.

4. The wound dressing of claim 1 wherein the microparticles when in a substantially nonhydrated form have an average particle size of 10 microns or less.

5. The wound dressing of claim 4 wherein the microparticles when in a substantially nonhydrated form have an average particle size of 1 micron or less.

6. The wound dressing of claim 5 wherein the microparticles when in a substantially nonhydrated form have an average particle size of 0.5 micron or less.

7. The wound dressing of claim 1 wherein the apertured liquid permeable substrate comprises 1 to 225 apertures per square centimeter.

8. The wound dressing of claim 1 wherein the apertured liquid permeable substrate comprises apertures having an average opening size of 0.1 millimeter to 0.5 centimeter.

9. The wound dressing of claim 1 wherein the microparticles comprise an amine-containing organic polymer.

10. The wound dressing of claim 9 wherein the amine-containing organic polymer microparticles comprise a quaternary ammonium salt of an organic polymer.

11. The wound dressing of claim 10 wherein the microparticles comprise a cationic homopolymer of the methyl chloride quaternary salt of 2-(dimethylamino)ethyl methacrylate.

12. The wound dressing of claim 1 wherein the microparticles comprise a copolymer of sodium acrylate and acrylic acid.

13. The wound dressing of claim 1 wherein the microparticles are in the form of a dispersion.

14. The wound dressing of claim 1 wherein the polymer composition further comprises a bioactive agent.

15. The wound dressing of claim 14 wherein the bioactive agent is an antimicrobial agent.

16. The wound dressing of claim 1 wherein the polymer composition further comprises an additive selected from the group consisting of a tackifier, a crosslinking agent, a stabilizer, a compatibilizer, an extruding aid, a filler, a pigment, a dye, a swelling agent, a chain transfer agent, and combinations thereof.

17. The wound dressing of claim 1 wherein the hydrophobic organic polymer matrix comprises a mixture of two or more polymers.

18. The wound dressing of claim 1 wherein the microparticles are present in an amount of 1 wt-% to 60 wt-%, based on the total weight of the polymer composition.

19. A wound dressing comprising an apertured liquid permeable substrate and an absorbent, nonadherent polymer composition comprising:

a hydrophobic organic polymer matrix comprising a styrene-isoprene-styrene copolymer, a styrene-butadiene-styrene copolymer, or mixtures thereof;

an optional plasticizing agent; and

hydrophilic microparticles comprising an amine-containing organic polymer.

20. A wound dressing comprising an apertured liquid permeable substrate and an absorbent, nonadherent polymer composition comprising:

a hydrophobic organic polymer matrix comprising a styrene-isoprene-styrene copolymer, a styrene-butadiene-styrene copolymer, or mixtures thereof;

an optional plasticizing agent; and

hydrophilic microparticles comprising a sodium polyacrylate copolymer.

21. A method of treating a wound, the method comprising applying the wound dressing of claim 1 to the wound.

22. A method of treating a wound, the method comprising applying the wound dressing of claim 19 to the wound.

23. A method of treating a wound, the method comprising applying the wound dressing of claim 20 to the wound.

INTERNATIONAL SEARCH REPORT

PCT/US2004/040707

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/58 A61L15/42 A61L15/22 A61L15/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/066087 A (COLOPLAST A/S; LYKKE, MADS) 29 August 2002 (2002-08-29) page 9, line 1 - page 10, line 7 page 11, line 11 - line 20 example 2 claims	1-23
P,X	WO 2004/080498 A (3M INNOVATIVE PROPERTIES COMPANY; HYDE, PATRICK, D; MENZIES, ROBERT, H) 23 September 2004 (2004-09-23) page 22, line 1 - line 24 tables 1,3,7,9 examples claims	1-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2005	11/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Thornton, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/080499 A (3M INNOVATIVE PROPERTIES COMPANY; BURTON, SCOTT, A; HYDE, PATRICK, D) 23 September 2004 (2004-09-23) page 17, line 23 - page 19, line 2 claims examples	1-23

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02066087 A	29-08-2002	CA 2438875 A1	29-08-2002
		CN 1492770 A-	28-04-2004
		WO 02066087 A1	29-08-2002
		EP 1361904 A1	19-11-2003
		HU 0303168 A2	29-12-2003
		JP 2004527600 T	09-09-2004
		US 2004065232 A1	08-04-2004
WO 2004080498 A	23-09-2004	WO 2004080498 A1	23-09-2004
WO 2004080499 A	23-09-2004	US 2004180093 A1	16-09-2004
		WO 2004080499 A1	23-09-2004

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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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(54) Title: POLYMER COMPOSITIONS WITH BIOACTIVE AGENT, MEDICAL ARTICLES, AND METHODS

(57) Abstract: A polymer composition that includes a hydrophilic polymer, an optional secondary organic polymer, and a bioactive agent distributed therein, wherein the bioactive agent is selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof.

WO 2005/056070 A1

POLYMER COMPOSITIONS WITH BIOACTIVE AGENT, MEDICAL ARTICLES, AND METHODS

BACKGROUND

Polymer compositions that include bioactive agents (e.g., antimicrobial agents) are used for a variety of applications, particularly medical applications such as wound dressings and wound packing materials. Conventional antimicrobial agents include ionizable silver compounds (e.g., silver salts such as silver nitrate); however, they are typically not light stable and leave a stain on skin with which they come into contact. Thus, stable antimicrobial polymer compositions are desired.

SUMMARY

The present invention is directed to polymer compositions, and methods of making and using them, that include a sparingly soluble silver compound, a copper compound, a zinc compound, or combinations thereof. Of these, it is more typically a silver compound. Such compositions are useful in medical articles, particularly wound dressings, wound packing materials, topical creams, and topical lotions, although a wide variety of other products can incorporate the polymer compositions. Such compositions are preferably stable. By this it is meant that the compositions are stable to at least one of the following types of radiation: visible light, ultraviolet light, electron beam, and gamma ray sterilization.

In one embodiment, the polymer composition comprises a hydrophilic polymer and a bioactive agent selected from the group consisting of a metal oxide of silver, copper, zinc, and combinations thereof. The bioactive agent has a particle size less than one micron and is dispersed within the hydrophilic polymer.

In certain embodiments, the hydrophilic polymer is an amine-containing organic polymer selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof. In certain embodiments, the hydrophilic polymer is a carboxylic acid-containing organic polymer.

In another embodiment, the polymer composition is preparable by a method comprising combining the hydrophilic polymer; a metal compound selected from the group consisting of a silver compound, a copper compound, a zinc compound, and

combinations thereof, wherein the silver compound has a solubility of at least 0.1 gram per liter in water; and a hydroxide source that converts the metal compound to the corresponding metal oxide. The components are combined in a manner to disperse the metal oxide within the hydrophilic polymer.

In another embodiment, the polymer composition is preparable by a method comprising combining the hydrophilic polymer; an ammonia source; a metal oxide selected from the group consisting of silver oxides, copper oxides, zinc oxide, and combinations thereof. The metal oxide dispersed within the hydrophilic polymer has a particle size less than one micron. The ammonia source can be ammonia and/or ammonium salts. When combined, the ammonia and metal oxide form an ammonia-metal complex with a solubility greater than 0.1 gram per liter in water.

In one embodiment, the polymer composition is preparable by a method comprising combining a dispersion comprising absorbent hydrophilic microparticles; a metal compound selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility of at least 0.1 gram per liter in water; and a hydroxide source that converts the metal compound to the corresponding metal oxide. The components are combined in a manner to incorporate the metal oxide within the microparticles. The microparticles when in a substantially nonhydrated form have an average particle size of 10 microns or less.

In another embodiment, a polymer composition is preparable by a method comprising combining an organic polymer matrix; a dispersion comprising absorbent hydrophilic microparticles; a metal compound selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility of at least 0.1 gram per liter of water; and a hydroxide source that converts the metal compound to the corresponding metal oxide. The metal oxide is incorporated within the microparticles. The organic polymer matrix preferably comprises a hydrophobic polymer.

In another embodiment, the hydrophilic polymer is an amine-containing polymer selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof.

Preferably, the polymer composition optionally includes a second organic polymer, thereby forming a mixture or blend of polymers. The second organic polymer

is preferably a hydrophobic material. In one embodiment, the hydrophobic material forms a continuous matrix and the hydrophilic polymer forms a discontinuous phase (e.g., microparticles). In another embodiment, the hydrophobic material forms a discontinuous phase and the hydrophilic polymer forms a continuous matrix. In still another embodiment, the hydrophobic material forms a bi-continuous or co-continuous phase with the hydrophilic amine-containing polymer.

In another aspect, methods of making the polymer compositions are also provided. In one embodiment, the method comprises combining a dispersion comprising hydrophilic organic microparticles with water and a metal compound under conditions effective to distribute substantially all of the metal compound in the hydrophilic organic microparticles, wherein the metal compound is selected from the group consisting of a silver compound with a solubility of at least 0.1 gram per liter in water, a copper compound, a zinc compound, and combinations thereof; adding a hydroxide source to convert the metal compound to the corresponding metal oxide; optionally adding a secondary organic polymer to the dispersion; and optionally removing a substantial portion of the water. The method can also include combining an oxidizing agent to form a higher valence metal oxide.

In another embodiment, the method comprises combining monomers for a hydrophilic organic polymer with a metal compound under conditions effective to polymerize the monomers and distribute substantially all of the metal compound within the hydrophilic organic polymer, wherein the metal compound is selected from the group consisting of a silver compound with a solubility of at least 0.1 gram per liter in water, a copper compound, a zinc compound, and combinations thereof; adding a hydroxide source to convert the metal compound to the corresponding metal oxide; and optionally adding a secondary organic polymer to the hydrophilic organic polymer.

In another embodiment, the method comprises combining a hydrophilic polymer; an ammonia source; and a metal oxide selected from the group consisting of silver oxides, copper oxides, zinc oxide, and combinations thereof. The metal oxide dispersed within the hydrophilic polymer has a particle size of less than one micron.

The present invention also provides medical articles that include the polymer compositions. The medical articles can be any of a wide variety of products, but preferably are wound dressings, wound packing materials, topical creams, or topical lotions.

In certain embodiments, the present invention provides a wound dressing that includes an apertured liquid permeable substrate and a nonadherent composition of the present invention.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably. Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

As used herein, "solubility" is presumed to be solubility in water at room temperature, typically 23 °C.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides polymer compositions that include a hydrophilic polymer, an optional second organic polymer, and a bioactive agent dispersed therein. The polymer composition can be in a wide variety of forms, such as an extruded film (e.g., having a thickness of 0.5 millimeter (mm) to 10 mm), a coating, a foam, particles, a hydrocolloid (i.e., a material that contains particles dispersed in a second phase, typically, hydrophilic particles dispersed in a lipophilic phase), a gel, a lotion, a cream, a molded article, etc.

In certain embodiments, the hydrophilic polymer is an amine-containing polymer selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof. In certain embodiments, the hydrophilic polymer is a carboxylic acid-containing organic polymer. In certain embodiments, the hydrophilic polymer is in the form of microparticles. The second organic polymer in certain embodiments forms a continuous matrix, and in certain embodiments is a hydrophobic material.

The bioactive agent is typically a metal compound selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof. Of these, it is more typically a silver compound. In certain embodiments, the polymer composition is preparable from a dispersion that includes

absorbent hydrophilic microparticles. In other embodiments, the polymer composition further comprises an organic polymer matrix.

The compositions of the present invention are preferably stable. By this it is meant that the compositions are stable to at least one of the following types of radiation: visible light, ultraviolet light, electron beam, and gamma ray sterilization. Such compositions are useful in medical articles, particularly wound dressings, wound packing materials, topical creams, and topical lotions, although a wide variety of other products can incorporate the polymer compositions. The wound dressings can be used in their hydrated or swollen forms if desired.

In certain embodiments, the compositions of the present invention are nonadherent, although it should be understood that an adhesive (e.g., a pressure sensitive adhesive) could be added to an article that includes the composition. As used herein, the nonadherent compositions of the present invention coated on a substrate display a 180° peel strength of less than 1 N/cm from steel according the to test procedure described in the Examples Section. Preferably, the compositions of the present invention do not adhere significantly to wound tissue such that they do not cause pain and/or destruction of the wound tissue upon removal.

HYDROPHILIC POLYMERS

The hydrophilic polymers can include anionic, cationic, amphoteric, non-ionic polymers, or combinations thereof. Typically, the type and amount of polymers are selected to provide the desired absorbency to the polymer composition of the present invention.

Preferably, the hydrophilic polymer has a weight average molecular weight of at least 1000. Preferably, the polymer is also dermatologically acceptable and non-reactive with the skin of the patient or with other components of the composition including any antimicrobial agents that may be present in therein.

Hydrophilic polymers (i.e., having an affinity for, absorbing, wetting smoothly with, tendency to combine with, or capable of dissolving in water) useful in the present invention may be made from a wide variety of synthetically prepared polymers, naturally occurring polymers, or chemically modified naturally occurring hydrophilic polymers. Varieties of polymers that can be used include synthetic polymers prepared

from single or multiple monomers. The hydrophilic polymers can be in a dispersion, such as a dispersion that includes absorbent hydrophilic microparticles.

Non-limiting examples of such polymers include: polyhydroxyalkyl acrylates and methacrylates (e.g., those prepared from 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, 2-hydroxypropyl acrylate, 2-hydroxypropyl methacrylate, 2,3-dihydroxypropyl methacrylate); poly(meth)acrylic acid and salts thereof (wherein (meth)acrylic acid refers to methacrylic acid and acrylic acid); polyvinyl lactams (e.g., those prepared from N-vinyl lactams such as N-vinyl-2-pyrrolidone, 5-methyl-N-vinyl-2-pyrrolidone, 5-ethyl-N-vinyl-2-pyrrolidone, 3,3-dimethyl-N-vinyl-2-pyrrolidone, 3-methyl-N-vinyl-2-pyrrolidone, 3-ethyl-N-vinyl-2-pyrrolidone, 4-methyl-N-vinyl-2-pyrrolidone, 4-ethyl-N-vinyl-2-pyrrolidone, N-vinyl-2-valerolactam, and N-vinyl-2-caprolactam); polyvinyl alcohols; polyoxyalkylenes; polyacrylamides; polystyrene sulfonates, natural or synthetically modified polysaccarides (e.g., starch, glycogen, hemicelluloses, pentosans, gelatin, celluloses, pectin, chitosan, and chitin), alginates, gums (e.g., Locust Bean, Guar, Agar, Carrageenan, Xanthan, Karaya, alginates, tragacanth, Ghatti, and Furcelleran gums), cellulosics (e.g., those prepared from methyl cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose and its salts, and hydroxypropyl cellulose); polymers prepared from water soluble amides (e.g., N-(hydroxymethyl)acrylamide and N-methacrylamide, N-(3-hydroxpropyl)acrylamide, N-(2-hydroxyethyl) methacrylamide, N-(1,1-dimethyl-3-oxabutyl)acrylamide N-[2-(dimethylamine)ethylacrylamide and -methacrylamide, N-[3-(dimethylamino)-2-hydroxylpropyllmethacrylamide, and N-[1,1-dimethyl-2-(hydroxymethyl)-3-oxabutyllacrylamide)); polymers prepared from water-soluble hydrazine derivatives (e.g., trialkylamine methacrylimide, and dimethyl-(2-hydroxypropyl)amine methacrylimide); mono-olefinic sulfonic acids and their salts, (such as sodium ethylene sulfonate, sodium styrene sulfonate and 2-acrylamideo-2-methylpropanesulfonic acid)). Other polymers include those prepared from the following monomers containing nitrogen in the non-cyclic or cyclic backbone of the monomer: 1-vinyl-imidazole, 1-vinyl-indole, 2-vinyl imidazole, 4(5)-vinyl-imidazole, 2-vinyl-l-methyl-imidazole, 5-vinyl-pyrazoline, 3-methyl-5-isopropenyl-pyrazole, 5-methylene-hydantoin, 3-vinyl-2-oxazolidone, 3-methacrylyl-2-oxazolidone, 3-methacrylyl-5-methyl-2-oxazolidone, 3-vinyl-5-methyl-2-oxazolidone, 2- and 4-vinyl-pyridine, 5-vinyl-2-methyl-pyridine, 2-

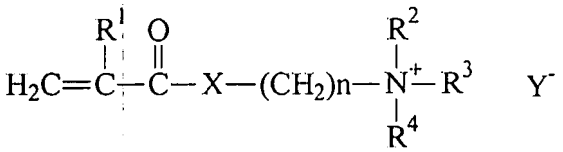
vinyl-pyridine-l-oxide, 3-isopropenyl-pyridine, 2- and 4-vinyl-piperidine, 2- and 4-vinyl-quinoline, 2,4-dimethyl-6-vinyl-s-triazine, and 4-acrylyl-morpholine.

For certain embodiments, the hydrophilic polymers are prepared with amine-containing organic polymers. The amine-containing organic polymers include poly(quaternary amines), polylactams, polyamides, and combinations thereof (including blends, mixtures, or copolymers thereof).

Preferably, the amine-containing polymer has a weight average molecular weight of at least 1000. Examples include, but are not limited to, polyvinyl pyrrolidone, polyvinyl caprolactam, poly-N-vinylacetamide, poly-N-vinyl formamide, polyacrylamide, and the like.

Preferably, the amine-containing organic polymer includes a quaternary amine, and more preferably, the amine-containing polymer is a quaternary ammonium salt of an organic polymer. Such polymers are preferred typically because they can stabilize the bioactive compounds (particularly, silver compounds) effectively, they provide good release of the bioactive compounds, and they are absorbing of water or bodily fluids (e.g., wound exudate). Examples include, but are not limited to, polymerization products of cationic vinyl monomers as disclosed in EP 0 489 967 A1, and inherently antimicrobial quaternary amine polymers as described in U.S. Pat. No. 6,039,940.

Other suitable amine-containing polymers can be prepared from a quaternary ammonium monomer, which is a salt having an organo-ammonium group and a monoethylenically unsaturated group. For certain embodiments, the quaternary ammonium monomer has the following general Formula (I):



Formula (I)

wherein: n is 2 to 10, preferably 2 to 3; R^1 is H or CH_3; R^2, R^3, and R^4 are each independently linear or branched organic groups, preferably having 1 to 16 carbon atoms (on average); X is O or NH; and Y^- is an acceptable anionic counterion to the N^+ of the quaternary ammonium group (e.g., one that does not adversely affect the

polymerization of the monomers or antimicrobial activity of an added antimicrobial agent).

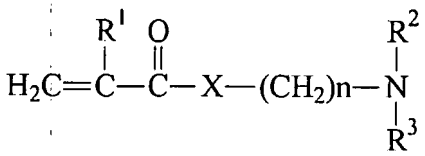
Preferably, R^2, R^3, and R^4 are each independently alkyl, aryl, alkaryl, or aralkyl groups. Alkyl groups are preferably lower alkyl, having 1 to 16 carbon atoms (on average) with methyl and ethyl groups being particularly preferred. Aryl is preferably phenyl but can be any suitable aromatic moiety such as those selected from the group consisting of phenyl, thiophenyl, naphthyl, biphenyl, pyridyl, pyrimidinyl, pyrazyl, pyridazinyl, furyl, thienyl, pyrryl, quinolinyl, bipyridyl, and the like. Representative of an aralkyl grouping is benzyl and representative of an alkaryl grouping is tolyl. X is preferably O. Representative counterions (Y^-) are Cl^-, Br^-, HSO_4^-, $CH_3CH_2OSO_3^-$, and $CH_3OSO_3^-$, with the chloride salts being particularly preferred. Alkyl groups can be straight or branched chain and alkyl and aryl groups can be substituted by non-interfering substituents that do not obstruct with the functionality of the polymers.

Useful copolymerizable quaternary ammonium monomers include, but are not limited to, those selected from 2-(meth)acryloxyethyl trialkyl ammonium halides and sulfates, and mixtures thereof. Examples of such compounds include, but are not limited to, 2-(meth)acryloxyethyl trimethyl ammonium chloride, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_3Cl$; 2-(meth)acryloxyethyl trimethyl ammonium methyl sulfate, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_3OSO_2OCH_3$; 2-(meth)acryloxyethyl methyl diethyl ammonium methyl sulfate, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)(C_2H_5)_2OSO_2OCH_3$; 2-(meth)acryloxyethyl dimethyl benzyl ammonium chloride, CH_2=C(H or CH_3)$CO_2CH_2CH_2N(CH_3)_2(C_6H_5CH_2)Cl$ (all of the preceding monomers available from Ciba Specialty Chemicals, Woodbridge, NJ); 2-(methylacryloxy)ethyl dimethyl hexadecyl ammonium bromide, CH_2=C(CH_3)$CO_2CH_2CH_2N(CH_3)_2(C_{16}H_{33})Br$ (described in U.S. Pat. No. 5,437,932 (Ali et al.)); and the like. Various combinations of these monomers can be used if desired.

Due to their availability, effectiveness in reinforcing (meth)acrylate polymers, and their antimicrobial activity, particularly preferred quaternary ammonium monomers are 2-acryloxyethyl trimethyl ammonium methyl chloride and 2-acryloxyethyl methyl diethyl ammonium methyl chloride. Such monomers are typically hydrophilic. Various combinations of other monoethylenically unsaturated monomers that are reinforcing monomers can be used in the polymers of the present invention. Such reinforcing

monomers include, but are not limited to, acrylic acid, methacrylic acid, ethylene vinyl acetate, and N,N-dimethylacrylamide.

As an alternative approach to providing polymers that contain a quaternary ammonium functional unit, it is possible to start with an amine monomer and form the quaternary ammonium unit following polymerization. For certain embodiments, the amine monomers have the following general Formula (II):



Formula (II)

wherein n, R^1, R^2, R^3, and X are the same as defined for Formula (I).

For certain embodiments, the hydrophilic polymers are prepared from carboxylic acid-containing organic polymers. Examples of such polymers include sodium polyacrylate (i.e., a copolymer of sodium acrylate and acrylic acid) microparticles such as those commercially available under the trade designation SALCARE SC91 from Ciba Specialty Chemicals (High Point, NC).

For certain embodiments, the hydrophilic polymer is in the form of particles. If the hydrophilic polymer is in the form of particles, it is typically in the form of microparticles. Preferably, the microparticles, when in a substantially nonhydrated form, have an average particle size of 10 microns or less, and more preferably, 1 micron or less. Typically and preferably, the microparticles have an average particle size of 0.5 micron or more when in a substantially nonhydrated form. Preferred microparticles are as described in EP 172 724 A2 and EP 126 528 A2 made by reverse phase polymerization and have a dry particle size below 4 microns.

For certain embodiments, the hydrophilic polymer (which is preferably in the form of microparticles) is absorbent (e.g., capable of absorbing water or bodily fluids). More preferably, the hydrophilic polymer (which is preferably in the form of microparticles) is superabsorbent. In this context, "superabsorbent" means that the material will absorb at least 100% of its weight.

In certain embodiments, the hydrophilic polymer can be particles, preferably in the form of microparticles, in a dispersion. The hydrophilic particles are typically dispersed in a continuous hydrophobic phase.

One type of dispersion is provided as a continuous hydrophobic liquid phase (e.g., mineral oil) and hydrophilic polymer particles dispersed within the hydrophobic liquid phase. Suitable examples of such materials are described in EP 0 126 528 A2. Such a material is commercially available under the trade designation SALCARE from Ciba Specialty Chemicals (High Point, NC). Suitable examples include SALCARE SC95 and SC96 which include a cationic homopolymer of the methyl chloride quaternary salt of 2-(dimethylamino)ethyl methacrylate (CAS No. 26161-33-1). Other suitable examples include SALCARE SC91, a copolymer of sodium acrylate and acrylic acid.

Monomers can be polymerized using techniques such as solution polymerization, emulsion polymerization, bulk polymerization, suspension polymerization, and the like. In particular, emulsion polymerization and suspension polymerization are preferable because the molecular weight of the polymer becomes high; solution polymerization is preferable because the molecular weight distribution is comparatively narrow; and bulk polymerization is favorable because no solvent is used.

In such polymerizations, initiators can be used to generate free-radicals upon the application of activating energy such as those conventionally used in the polymerization of ethylenically unsaturated monomers. Included among useful free-radical initiators are the thermally activated initiators such as organic peroxides, organic hydroperoxides, and azo-compounds. Representative examples of such initiators include, but are not limited to, benzoyl peroxide, tertiary-butyl perbenzoate, diisopropyl peroxydicarbonate, cumene hydroperoxide, azobis(isobutyronitrile), and the like. Generally, the thermal initiators are typically used in amounts from 0.01 to 5 percent by weight of monomer.

The polymerization of the polymer may also be initiated by photoinitiators. Such photochemically activated initiators are well known and have been described in the polymerization art; e.g., Chapter II of "Photochemistry" by Calvert and Pitts, John Wiley and Sons (1966) and in *Progress in Organic Coatings, 13,* 123-150 (1985). Representative examples of such initiators include benzoin, benzoin methyl ether, benzoin isopropyl ether, benzoin isobutyl ether, and 2-hydroxy-2-methyl-1-phenyl-1-

propane, benzildimethylketal and benzildiethylketal, 2-hydroxy-1-(4-(2-hydroxyethoxy)phenyl)-2-methyl-1-propanone. A presently preferred photoinitiator is 2-hydroxy-1-(4-(2-hydroxyethoxy)phenyl)-2-methyl-1-propanone. Generally, photoinitiators are used in amounts from 0.01 to 5 percent by weight of monomer.

The polymerization of the polymer may also be initiated by electromagnetic radiation such as electron beams and the gamma-rays of cobalt 60, and the like. The irradiation dose is typically between 1 and 100 kGy.

The polymer may be crosslinked by adding a crosslinking compound or through electron beam or gamma radiation. A crosslinking compound can be a multi-ethylenically unsaturated compound wherein the ethylenic groups are vinyl groups, allyl groups, and/or methallyl groups bonded to nitrogen or oxygen atoms. Exemplary compounds include divinyl, diallyl or dimethallyl esters (e.g., divinyl succinate, divinyl adipate, divinyl maleate, divinyl oxalate, divinyl malonate, divinyl glutarate, diallyl itaconate, diallyl maleate, diallyl fumarate, diallyl diglycolate, diallyl oxalate, diallyl adipate, diallyl succinate, diallyl azelate, diallyl malonate, diallyl glutarate, dimethallyl maleate, dimethallyl oxalate, dimethallyl malonate, dimethallyl succinate, dimethallyl glutarate, and dimethallyl adipate), divinyl, diallyl or dimethallyl ethers (e.g., diethyleneglycol divinyl ether, butanediol divinyl ether, ethylene glycol divinyl ether, ethylene glycol diallyl ether, diethylene glycol diallyl ether, butane diol diallyl ether, ethylene glycol dimethallyl ether, diethylene glycol dimethallyl ether, and butane diol dimethallyl ether), divinyl, diallyl or dimethallyl amides including bis(N-vinyl lactams), (e.g., 3,3'-ethylidene bis(N-vinyl-2-pyrrolidone)), and divinyl, diallyl or dimethallyl ureas.

The hydrophilic polymers can be used in a variety of combinations. The total amount of hydrophilic polymer(s) (e.g., microparticles) is preferably at least 1 percent by weight (wt-%), and more preferably, at least 5 wt-%, based on the total weight of the polymer composition. The total amount of hydrophilic polymer(s) (e.g., microparticles) is preferably at most 60 percent by weight (wt-%), based on the total weight of the polymer composition.

BIOACTIVE AGENT

The polymer compositions of the present invention typically include a bioactive agent that is a metal compound selected from the group consisting of a silver

compound, a copper compound, a zinc compound, and combinations thereof. When dispersed within the hydrophilic polymer, the silver, copper, and zinc compounds are typically in the form of metal oxides. The metal compounds are typically antimicrobial, although they can also demonstrate other activities, such as antifungal activity. Preferably, the bioactive agent is a silver compound.

Substantially all of the dispersed silver, zinc, and copper compounds have an average particle size less than 1 micron in size. By utilizing a process that solubilizes the metal compound, either through use of a soluble metal compound that is converted in-situ to the corresponding metal oxide with a hydroxide source, or by complexing the metal oxide using an ammonia source in situ, the resulting dispersed metal oxides form particles within the hydrophilic polymer. Average particles sizes less than 1 micron are provided in part by the tendency of the metal oxide to form a complex with the hydrophilic polymer. The small particle size allows accelerated dissolution based on the high surface area to mass ratio of the particle.

One or more bioactive agents of this type can be used. Herein, these are considered the primary bioactive agents. Optionally, one or more secondary bioactive agents (e.g., antimicrobial agents, antibiotics) can be used in combination with these primary bioactive agents. Preferred compositions have more than one bioactive agent.

The bioactive agent can be present in the polymer composition in an amount to produce a desired effect (e.g., antimicrobial effect). Preferably, the bioactive agent is present in an amount such that the polymer composition is stable. In this context, "stable" means the composition does not turn black over a typical exposure time in the presence of at least one of the following types of radiation: visible light, ultraviolet light, electron beam, and gamma ray sterilization.

A preferred molar ratio of the metal compound to hydrophilic monomers (for the embodiments that prepare the polymer *in situ*) is at least 1 mole metal compound to 500 moles hydrophilic monomer. Although there is essentially no upper limit, a preferred molar ratio is no more than 1 mole bioactive agent to 20 moles hydrophilic monomer.

A preferred weight ratio of the metal compound to hydrophilic polymers (for the embodiments that mix the metal compound with a previously prepared polymer) is at least 0.1 weight percent (more preferably at least 1 weight percent) metal compound based on the total weight of the hydrophilic polymer. Although there is essentially no

upper limit, a preferred weight ratio is no more than 10 weight percent (more preferably no more than 8 weight percent) metal compound based on the total weight of the hydrophilic polymer.

SECONDARY POLYMER

The polymer compositions can include one or more secondary organic polymers in addition to one or more hydrophilic polymers. These can be liquids or solids at room temperature. This secondary polymer can be hydrophobic or hydrophilic, although preferably it is hydrophobic (i.e., antagonistic to, shedding, tending not to combine with, or incapable of dissolving in water).

Examples of hydrophilic materials include, but are not limited to, polysaccharides, polyethers, polyurethanes, polyacrylates, cellulosics, and alginates.

Examples of hydrophobic materials include, but are not limited to, polyisobutylene, polyethylene-propylene rubber, polyethylene-propylene diene-modified (EPDM) rubber, polyisoprene, styrene-isoprene-styrene, styrene-butadiene-styrene, styrene-ethylene-propylene-styrene, and styrene-ethylene-butylene-styrene. Hydrophobic materials are particularly desirable for nonadherent compositions and articles. Particularly preferred hydrophobic materials include styrene-isoprene-styrene and styrene-ethylene-butylene-styrene, and even more preferred materials include styrene-isoprene-styrene.

The secondary polymer can be in the form of a continuous matrix (i.e., phase) or a discontinuous matrix (e.g., in the form of particles). It can form a bi-continuous or co-continuous phase with the primary hydrophilic polymer. The secondary organic polymer can be elastomeric, thermoplastic, or both.

Elastomeric polymers useful as optional secondary polymers in the invention are typically materials that form one phase at 21°C, have a glass transition temperature less than 0°C, and exhibit elastomeric properties. The elastomeric polymers include, but are not limited to, polyisoprenes, styrene-diene block copolymers, natural rubber, polyurethanes, polyether-block-amides, poly-alpha-olefins, (C1-C20) acrylic esters of meth(acrylic) acid, ethylene-octene copolymers, and combinations thereof.

Elastomeric materials useful in the present invention include, for example, natural rubbers such as CV-60 (a controlled viscosity grade natural rubber having Mooney viscosity of 60 +/- 5 ML, 1+4 at 100°C, available as an International

commodity); butyl rubbers, such as Exxon Butyl 268 available from Exxon Chemical Co., Houston, Texas; synthetic poly-isoprenes such as CARIFLEX IR309, available from Kraton Polymers, Houston, Texas, and NATSYN 2210, available from Goodyear Tire and Rubber Co., Akron, Ohio; ethylene-propylenes; polybutadienes; polyisobutylenes such as VISTANEX MM L-80, available from ExxonMobil Chemical Co.; and styrene-butadiene random copolymer rubbers such as AMERIPOL 1011A, available from BF Goodrich of Akron, Ohio.

Thermoplastic polymers useful as optional secondary polymers in the invention include, for example, polyolefins such as isotactic polypropylene; low density or linear low density polyethylene; medium density polyethylene; high density polyethylene; polybutylene; polyolefin copolymers or terpolymers, such as ethylene/propylene copolymer and blends thereof; ethylene-vinyl acetate copolymers such as ELVAX 260, available from E. I. DuPont de Nemours & Co., Wilmington, Delaware; ethylene acrylic acid copolymers; ethylene methacrylic acid copolymers such as SURLYN 1702, available from E. I. DuPont de Nemours & Co.; polymethylmethacrylate; polystyrene; ethylene vinyl alcohol; polyester; amorphous polyester; polyamides; fluorinated thermoplastics such a polyvinylidene fluoride; polytetrafluoroethylene; fluorinated ethylene/propylene copolymers; halogenated thermoplastics such as a chlorinated polyethylene; and combinations thereof. Other exemplary thermoplastic polymers are disclosed in International Publication No. WO 97/23577.

Thermoplastic elastomeric polymers useful as optional secondary polymers in the invention are typically materials that form at least two phases at 21°C, flow at a temperature greater than 50°C and exhibit elastomeric properties. Thermoplastic elastomeric materials useful in the present invention include, for example, linear, radial, star and tapered styrene-isoprene block copolymers such as KRATON D1107P, available from Kraton Polymers, and EUROPRENE SOL TE 9110, available from EniChem Elastomers Americas, Inc. Houston, Texas, linear styrene-(ethylene/butylene) block copolymers such as KRATON G1657 available from Kraton Polymers, linear styrene-(ethylene/propylene) block copolymers such as KRATON G1657X available from Kraton Polymers, styrene-isoprene-styrene block copolymers such as KRATON D1119P available from Kraton Polymers, linear, radial, and star styrene-butadiene block copolymers such as KRATON D1118X, available from Kraton Polymers, and EUROPRENE SOL TE 6205 available from EniChem Elastomers Americas, Inc.,

polyetheresters such as HYTREL G3548, available from E. I. DuPont de Nemours & Co., and poly-alpha-olefin based thermoplastic elastomeric materials such as those represented by the formula -(CH_2-CHR) where R is an alkyl group containing 2 to 10 carbon atoms and poly-alpha-olefins based on metallocene catalysis such as ENGAGE EG8200, an ethylene/l-octene copolymer available from DuPont Dow Elastomers Co., Wilmington, Delaware. Other exemplary thermoplastic elastomers are disclosed in International Publication No. WO 96/25469.

Various combinations of secondary organic polymers in various amounts can be used to produce desired effects. This can be readily determined by one of skill in the art based on the teachings herein.

OPTIONAL ADDITIVES

The polymer compositions of the present invention can include a wide variety of optional additives. Examples include, but are not limited to, secondary bioactive agents, secondary absorbent particles, foaming agents, swelling agents, fillers, pigments, dyes, plasticizers (for example, mineral oil and petrolatum), tackifiers, crosslinking agents, stabilizers, compatibilizers, extruding aids, chain transfer agents, and combinations thereof.

In addition to the bioactive agents described above (e.g., silver, copper, and zinc compounds), other (secondary) bioactive agents can be incorporated into the polymer compositions of the present invention. Examples include, but are not limited to, antimicrobial agents such as parachlorometaxylenol, chlorhexidine and salts thereof, iodine, and iodophores, and antibiotics such as neomycin, bacitracin, and polymyxin B. Preferred compositions have more than one bioactive agent.

In certain embodiments, polymer compositions of the present invention can include secondary absorbent particles. Such secondary particles can be a particle with an average particle size of greater than 10 microns when in a substantially nonhydrated form. Preferably, such particles are superabsorbent. Examples include, but are not limited to, those described in U.S. Pat. No. 5,369,155.

In certain embodiments, polymer compositions of the present invention can include a swelling agent, preferably a nonvolatile swelling agent. Examples of swelling agents include, but are not limited to, polyols, monosaccharides, ether alcohols, and combinations thereof. Specific examples are disclosed in U.S. Pat. No. 5,270,358.

In certain embodiments, polymer compositions of the present invention can include fillers, which can be inorganic or organic. Examples of inorganic fillers include, but are not limited to, barytes, chalk, gypsum, kieserite, sodium carbonate, titanium dioxide, cerium oxide, silica dioxide, kaolin, carbon black, and hollow glass microbeads. Examples of organic fillers include, but are not limited to, powders based on polystyrene, polyvinyl chloride, urea-formaldehyde, and polyethylene. The fillers may be in the form of fibers, such as chopped fibers. Examples of suitable chopped fibers include glass fibers (typically 0.1 millimeter (mm) to 1 mm long) or fibers of organic origin such as, for example, polyester or polyamide fibers.

In order to confer color to the polymer compositions it is possible to use dyes or colored pigments of an organic or inorganic basis such as, for example, iron oxide or chromium oxide pigments or phthalocyanine- or monoazo-based pigments.

METHODS OF PREPARATION OF POLYMER COMPOSITIONS AND ARTICLES

Whether starting with monomers and polymerizing the monomers in the presence of the bioactive agent, or adding a bioactive agent to a previously prepared polymer, the components are combined in a manner to produce a polymer composition having a bioactive agent dispersed therein.

The bioactive agent used to prepare the compositions of the present invention are chosen from silver compounds, zinc compounds and copper compounds, and combinations thereof. In one embodiment, at least the silver compound has a solubility in water of at least 0.1 gram per liter, and more preferably, the silver, copper, and zinc compounds each have a solubility in water of at least 0.1 gram per liter. Sufficient solubility, i.e., solubility of at least 0.1 gram per liter in water, is desirable such that the compounds are dissolved into the hydrophilic polymer phase. Examples of such metal compounds include, but are not limited to, silver nitrate, silver acetate, silver lactate, silver sulfate, copper chloride, copper nitrate, copper acetate, copper lactate, copper sulfate, zinc chloride, zinc nitrate, zinc acetate, zinc lactate, and zinc sulfate.

When using a metal compound soluble in the hydrophilic phase, a hydroxide source is added to convert the silver, zinc, and/or copper compound to the corresponding metal oxide. Suitable hydroxide sources include but are not limited to sodium hydroxide, potassium hydroxide, and calcium hydroxide. In preferred

embodiments, and particularly those used in medical applications, the hydroxide source is sodium hydroxide.

In another embodiment, the metal compound has insufficient solubility, i.e., less than 0.1 g per liter of water, to allow dispersion of the metal compound in the hydrophilic polymer. Examples of such metal compounds include, but are not limited to, silver oxide, silver chloride, zinc oxide, copper oxide. In those instances, the metal compound is dissolved in ammonia or an ammonium compound, which forms a complex with the ammonia that is soluble in the hydrophilic phase. Suitable ammonia sources include ammonia, and ammonium salts such as ammonium pentaborate, ammonium acetate, ammonium carbonate, ammonium peroxyborate, ammonium tertraborate, triammonium citrate, ammonium carbamate, ammonium bicarbonate, ammonium malate, ammonium nitrate, ammonium nitrite, ammonium succinate, ammonium sulfate, ammonium tartarate, and mixtures thereof.

In another embodiment, the metal compound with low solubility can be dissolved in a strong acid such as nitric acid or sulfuric acid. The metal compound forms a soluble salt that will disperse in the hydrophilic polymer. A neutralizing agent, such as sodium hydroxide or ammonium hydroxide, can be added to neutralize the strong acid.

In some embodiments, higher valence metal oxide, for example, where the oxidation state of silver is Ag (II), Ag(III), or Ag(IV), may be desired. The valence state of the metal oxide can be increased by the addition of an oxidizing agent. Suitable oxidizing agents include hydrogen peroxide and alkali metal persulfates such as sodium persulfate, as discussed in U.S. Patent No. 6,436,420 to Antelman. Other suitable oxidizing agents include permanganates, hypochlorites, perchlorates, and nitric acid.

The components are combined in a manner to produce a polymer composition wherein the bioactive agent, i.e., the metal compound, is incorporated within the hydrophilic polymer. Preferably, this results from combining the components in the presence of water (e.g., 1-20 wt-%, based on the total weight of the composition) and then optionally removing a substantial portion of the water (such that less than 1 wt-% water is remaining, based on the total weight of the composition). If desired, all the water can be removed.

In certain embodiments, a dispersion that includes hydrophilic organic microparticles is combined with water, a metal compound, a hydroxide source, and

optionally an oxidizing agent under conditions effective to disperse (preferably, dissolve) the metal compound in the hydrophilic organic microparticles. Optionally, a secondary organic polymer can be added to the mixture of the dispersion, water, hydroxide source and bioactive agent. Once sufficiently mixed to impregnate at least a portion of the bioactive agent (e.g., silver compound) into the hydrophilic particles, the water is removed if desired.

In certain embodiments, a dispersion that includes hydrophilic organic microparticles is combined with water, a metal compound with low solubility, i.e., less than 0.1 g per liter in water, an ammonia source, and optionally an oxidizing agent under conditions effective to disperse (preferably, dissolve) the metal agent in the hydrophilic organic microparticles. Optionally, a secondary organic polymer can be added to the mixture of the dispersion, water, ammonia source and metal compound with low solubility. Once sufficiently mixed to impregnate at least a portion of the insoluble bioactive agent (e.g., silver compound) into the hydrophilic particles, the ammonia is removed, and the water is removed if desired.

In other embodiments, monomers for a hydrophilic organic polymer are combined with a soluble form of the metal compound under conditions effective to polymerize the monomers and distribute (preferably dissolve) at least a portion of the metal in the hydrophilic organic polymer. The soluble form of the metal compound can be present during the polymerization process or added after the polymerization is complete. Once dispersed, the soluble form of the metal compound can be converted to the corresponding metal oxide. Optionally, a secondary organic polymer can be added to the hydrophilic organic polymer with the bioactive agent distributed therein.

The polymer compositions with the bioactive agent therein can be melt processed (e.g., extruded or molded) or solvent cast to form the desired products (e.g., wound dressing).

The materials used to prepare the polymer compositions of the present invention are melt processable if they are fluid or pumpable, and they do not significantly degrade or gel at the temperatures used to melt process (e.g., extruding or compounding) the composition (e.g., at least 50°C and up to 300°C). Preferably, such materials have a melt viscosity of at least 10 poise and often up to 1,000,000 poise, as measured by capillary melt rheometry at the processing temperatures and shear rates employed in extrusion. Typically, suitable materials possess a melt viscosity within this

range at a temperature of at least 175°C and often up to 225°C and a shear rate of 100 seconds^{-1}.

Continuous melt process forming methods include drawing the extruded composition out of a film die and subsequently contacting a moving plastic web or other suitable backing. Another continuous forming method involves directly contacting the extruded composition to a rapidly moving plastic web or other suitable substrate. In this method, the extruded composition can be applied to a moving web using a die having flexible die lips such a reverse orifice coating die and other contact dies using rotating rods. The composition can also be extruded in the form of continuous fibers and blown micro-fiber webs as disclosed in Wente, Van A., "Superfine Thermoplastic Fibers," Industrial Engineering Chemistry, Vol. 48, pp. 1342-1346; Wente, Van A. et al., "Manufacture of Superfine Organic Fibers," Report No. 4364 of the Naval Research Laboratories, published May 25, 1954; U.S. Pat. No. 5,176,952 and U.S. Pat. No. 3,841,953. After melt process forming the composition is solidified by quenching using either direct methods, such as chill rolls or water baths, or indirect methods, such as air or gas impingement, or both.

In some embodiments, a non-adherent or adherent composition (which can be in the form of a gel) is preferably obtained by hot mixing without a solvent (so-called hot-melt process), by blending an elastomer with an oily plasticizer and antioxidants, and then by adding a hydrocolloid either as finely divided powder or as a dispersion. If active agents are provided, these may be added to either the elastomer or the hydrocolloid.

Articles can be prepared using compositions described herein according to a variety of methods, particularly coating methods. When a porous substrate is coated, the process of coating the porous substrate with the composition typically allows the yarns, filaments, or film to be properly trapped in the composition, while leaving most of the apertures unobstructed by the composition. Depending on the structure of the support used, the amount of composition employed will vary over a wide range (typically from 50 grams per square meter (g/m^2) to 300 g/m^2, and preferably from 60 g/m^2 to 160 g/m^2).

In certain embodiments, the coating can be carried out hot, without a solvent, using a continuous process in which the substrate is directed over a first coating roll covered with a layer of molten composition having a predetermined thickness, and then

over a second roll which removes the composition lying within the apertures of the substrate. The substrate thus covered with gel only on the yarns, filaments, or film is then cooled in a stream of air so that the composition cannot flow and remains uniformly distributed around the yarns, filaments, or film. If necessary, a system producing a laminar stream of air is provided, which system is able both to correct the distribution of the composition around the yarns, filaments, or film and to unblock any substrate apertures, which would not have been open in the previous step of the process.

According to a variant of this process, a substrate can be passed through a bath of molten polymeric composition (for example, at a temperature of 120°C to 200°C). The substrate covered with molten composition is then passed between two fixed rolls pressed against each other with a predetermined gap, so as to remove the excess composition. The amount of composition remaining on the yarns, filaments, or film depends essentially on the gap set between the fixed rolls. The covered process is then cooled and treated in a manner similar to the previous process.

If desired, the cooled coated substrate can be covered with two protective films (for example, thin polyester films). These films may or may not require a nonstick treatment and can function to facilitate extraction from a package and in handling the article. If desired, the coated substrate can be cut into individual compresses, of sizes suitable for the use, packaged in sealed sachets, and sterilized.

Solvent casting may also be used to prepare the articles of the present invention. This method typically employs a common solvent, selected for compatibility with the polymer composition components. Such common solvents include, for example, toluene and tetrahydrofuran. Specific selection of a common solvent for a particular subset of the present invention is within the skill of the art. In the solvent casting method, the materials included in the composition are blended to form a uniform mixture, then coated onto a carrier web or a backing (described below) using a known coating technique such as gravure coating, curtain coating, die coating, knife coating, roll coating, or spray coating. A preferred coating method is knife coating. The solvent is then removed from the coated backing, usually with the aid of a drying oven for a time and temperature selected to remove any undesirable level of residual solvent.

In some embodiments, a composition containing a silver oxide can be coated on the polymer composition as described in applicants co-pending application, Ser. No.

10/728,446. The metal oxide is dissolved in solution by complexing the metal compound in an ammonium salt. Suitable ammonium salts include ammonium pentaborate, ammonium acetate, ammonium carbonate, ammonium peroxyborate, ammonium tertraborate, triammonium citrate, ammonium carbamate, ammonium bicarbonate, ammonium malate, ammonium nitrate, ammonium nitrite, ammonium succinate, ammonium sulfate, ammonium tartarate, and mixtures thereof. The resultant solution can be coated at less than 40 °C, and dried at temperatures less than 160 °C. Once dried, the substrate remains coated with the metal oxide.

In a preferred embodiment, the solution is formed from the combination of silver oxide and ammonium carbonate. The coated substrate is subsequently dried, optionally in the presence of heat. Ammonia and carbon dioxide are driven off, leaving essentially the silver oxide remaining on the substrate.

Layered constructions can also be prepared using lamination, coating, or extrusion techniques known to one of skill in the art and as described, for example, in U.S. Pat. No. 6,379,791.

If desired, compositions of the present invention can be sterilized. Methods of sterilization include treatment with electron beam or gamma radiation.

MEDICAL ARTICLES

The polymer compositions of the present invention can be used in a wide variety of products, although they are preferably used in medical articles. Such medical articles can be in the form of a wound dressing, wound packing material, or other material that is applied directly to or contacts a wound.

Such articles may or may not include a backing (i.e., a support substrate). If a backing or support substrate is desired, it can be porous or nonporous. The composition of the present invention can be coated on the support substrate or impregnated into it, for example.

Suitable materials are preferably flexible, and may be fabric, non-woven or woven polymeric films, metallic foils, paper, and/or combinations thereof. More specifically, film backings are useful with the polymer compositions of the present invention. For certain embodiments it is desirable to use a permeable (e.g., with respect to moisture vapor), open apertured substrate (i.e., a scrim). For certain embodiments it

is desirable to use an open- or closed-cell foam, such as that disclosed in U.S. Patent No. 6,548,727 to Swenson.

The substrates (i.e., backings) are preferably porous to allow the passage of wound fluids, moisture vapor, and air. In certain embodiments, the substrates are substantially impervious to liquid, especially wound exudate. In certain embodiments, the substrates are capable of absorbing liquid, especially wound exudate. In certain embodiments, the substrate is an apertured liquid permeable substrate.

Suitable porous substrates include knits, wovens (e.g., cheese cloth and gauze), nonwovens (including spun-bonded nonwovens), extruded porous sheets, and perforated sheets. The apertures (i.e., openings) in the porous substrates are of sufficient size and sufficient number to facilitate high breathability. For certain embodiments, the porous substrates have at least 1 aperture per square centimeter. For certain embodiments, the porous substrates have no greater than 225 apertures per square centimeter. For certain embodiments, the apertures have an average opening size (i.e., the largest dimension of the opening) of at least 0.1 millimeter (mm). For certain embodiments, the apertures have an average opening size (i.e., the largest dimension of the opening) of no greater than 0.5 cm.

For certain embodiments, the porous substrates have a basis weight of at least 5 grams/meter^2. For certain embodiments, the porous substrates have a basis weight of no greater than 200 grams/meter^2.

The porous substrates (i.e., backings) are preferably flexible yet resistant to tearing. For certain embodiments, the thickness of the porous substrates is at least 0.0125 mm. For certain embodiments, the thickness of the porous substrates is no greater than 3 mm.

Materials of the backing or support substrate include a wide variety of materials including paper, natural or synthetic fibers, threads and yarns made from materials such as cotton, rayon, wool, hemp, jute, nylon, polyesters, polyacetates, polyacrylics, alginates, ethylene-propylene-diene rubbers, natural rubber, polyesters, polyisobutylenes, polyolefins (e.g., polypropylene polyethylene, ethylene propylene copolymers, and ethylene butylene copolymers), polyurethanes (including polyurethane foams), vinyls including polyvinylchloride and ethylene-vinyl acetate, polyamides, polystyrenes, fiberglass, ceramic fibers, and/or combinations thereof.

The backing can also be provided with stretch-release properties. Stretch-release refers to the property of an adhesive article characterized in that, when the article is pulled from a surface, the article detaches from the surface without leaving significant visible residue. For example, a film backing can be formed from a highly extensible and highly elastic composition that includes elastomeric and thermoplastic A-B-A block copolymers, having a low rubber modulus, a lengthwise elongation to break of at least 200%, and a 50% rubber modulus of not above 2,000 pounds/square inch (13.8 megapascals (MPa)). Such backings are described in U.S. Pat. No. 4,024,312 (Korpman). Alternatively, the backing can be highly extensible and substantially non-recoverable such as those described in U.S. Pat. No. 5,516,581 (Kreckel et al.).

Pressure sensitive adhesives used in medical articles can be used in articles of the present invention. That is, a pressure sensitive adhesive material could be applied to the article of this invention, for example, around the periphery, to adhere the article to the skin.

In another aspect, the compositions of the present invention will be in the form of an aqueous gel. Suitable gelling agents include polyoxyethylene-polyoxypropylene diol block copolymers, polyacrylic acid lightly crosslinked with triallyl sucrose which has been neutralised using an alkali metal hydroxide, cellulosic derivatives such as carboxymethyl cellulose, hydroxymethyl cellulose, natural gums, and the like. It will be appreciated that care must be taken to avoid using gelling agents that are incompatible with the bioactive agent, such as the silver compounds. Suitable gel forming block copolymers of polyoxyethylene- polyoxypropylene will have a molecular weight from 4,600 to 13,500 (approximately) and will be present in the gel in an amount from 50% for the lower molecular weight copolymers to 20% for the higher molecular weight copolymers, so that the gel when applied topically is neither too stiff nor too fluid. Typically the gels are formed by mixing together the copolymer and water to form an aqueous solution at a temperature of 2°C and adding the bioactive agent (e.g., silver compound) and then allowing the solution to gel as it warms to ambient temperature. A preferred group of gelling agents are the polyoxyethylene-polyoxypropylene diol block copolymers which are commercially available under the trade designation PLURONICS from BASF-Wyandotte (e.g., PLURONICS F108, F127, and P105).

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Materials

KRATON D4433- a pre-compounded KRATON D1112 and mineral oil (77/23) blend, where the KRATON D1112 is a linear polystyrene-polyisoprene-polystyrene (SIS) thermoplastic elastomeric copolymer having 15 wt.% polystyrene. The blend is available from Kraton Polymers, Houston, Texas.

KRATON D1124K -radial 4-arm star polystyrene-polyisoprene $(SI)_4$ thermoplastic elastomeric copolymer having 30 wt.% polystyrene available from Kraton Polymers, Houston, Texas.

KAYDOL - mineral oil available from Crompton Corporation, formerly Witco Corporation.

IRGANOX 1010 – antioxidant available from Ciba Specialty Chemicals, Tarrytown, New York.

SALCARE SC91 – 50 wt-% solids cosmetic grade emulsion having micro-particles of chemically crosslinked hydrophilic anionic sodium acrylates copolymer in mineral and paraffin oils available from Ciba Specialty Chemicals, High Point, North Carolina.

SALCARE SC95 – 50 wt-% solids cosmetic grade emulsion having micro-particles of chemically crosslinked hydrophilic cationic quaternary ammonium acrylate polymer (methychloride quaternary ammonium salt of DMAEMA) in mineral and paraffin oils available from Ciba Specialty Chemicals, High Point, North Carolina.

Silver Nitrate ($AgNO_3$) – 99+% reagent grade from Aldrich (Milwaukee, Wisconsin) was used to make a 5.6M AgNO3 solution by dissolving the as received AgNO3 in water. One hundred (100) grams of de-ionized (DI) water and 95.2 grams of silver nitrate were dissolved to make a 5.6 molar (M) silver nitrate solution

Trypticase (Tryptic) Soy Broth (TSB)- medium available from Becton Dickinson & Company, Bedford, Massachusetts.

Polyester Knitted Fabric was a 24 mesh polyester knit ($61 g/m^2$) purchased from Lamports Filter Media, Inc, Cleveland, OH.

10% Hydrogen Peroxide Solution was made by diluting 100 grams of a 30 wt.% hydrogen peroxide (H_2O_2-available from Mallinckrodt, St Louis, MO) with 200 grams of de-ionized water to make a 10 wt.% H_2O_2 solution

5.6M NaOH solution was made by mixing 100 grams of DI water and 22.4 grams of sodium hydroxide to make a 5.6M NaOH solution.

Aqueous Silver (I) Oxide (Ag_2O) solution [1.3 wt.% Ag_2O, 4.4 wt.% $(NH4)_2CO_3$ and 94.3 wt.% water] made by mixing Ag_2O (Alfa Aesar, Ward Hill, MA) with ammonium carbonate solution until completely dissolved.

Ammonium carbonate, available from Mallinkrodt Baker, Inc., Phillipsburg, New Jersey.

Test Procedures

Antimicrobial Performance Tests

% Live Bacteria Test

The effectiveness of a sample was tested using a L-7012, Bacterial Viability Kit, available from Molecular Probes (Eugene, Oregon). The procedure is outlined below using the red, propidium iodide dye, and green, SYTO 9 dye, contained in the kit to stain the live and dead bacteria.

Preparation of bacteria solution: Staphylococcus aureus bacteria were grown in Trypticase (Tryptic) Soy Broth (TSB) medium overnight. Bacteria were concentrated by centrifugation at 10,000x gravity for 15 minutes (min). Supernatant was removed and the pellet was re-suspended in MilliQ water (filtered through a 0.2 μm pore-size filter) or in Butterfield phosphate buffer (from Hardy Diagnostics, Santa Maria, California). Bacteria solution was diluted to the desired bacteria concentration (10^7 cells/milliliters) by measuring the optical density (OD) at 670 nm. For a control experiment, the bacteria solution was incubated with 70% isopropyl alcohol at room temperature for 1 hour (hr) to measure the killed bacteria control. Different volume of live and dead bacteria solutions were mixed to generate a range of percent live solution for calibration purposes.

Bacteria labeling and Antimicrobial testing: 7 mls of bacteria solution at initial concentration of approximately $1x10^8$ bacteria/mls were pipetted into a 50 mls conical

tube containing the sample. At the specified time (e.g., 2 hr), 50 micro-liter (μL) of the supernatant was pipetted into fluorescent measurement tube which already contained 450 μL of MiliQ water and premixed green dye and red dye solution (1.5 μL dye mixture for 500 μL bacteria solution) was added and the mixture was incubated for 15 minutes in the dark at room temperature. These solutions were then measured by flow cytometry. Cell viability was measured using the BD FACS Caliber flow cytometer (made by Becton Dickinson & Company, Franklin Lakes, New Jersey). The flow cytometer is equipped with an argon-ion laser at 488 nanometers (nm) and 15 milliWatts (mW) output. Data acquisition and analysis were controlled using CellQuest software and PBPAC hardware interface. The light path contained a 488/10 nm blocking filter, then a 530/30 nm filter before the green PMT and a 585/42 nm long pass filter before the red PMT. The sampling rate was around 3000-7000 particles/second. The sheath fluid was FACSFlow by Becton Dickinson. The instrument voltage was 5.5 Volt.

The live cell and dead bacteria responses were established with the 100% live cell and 100% dead cell (for killed bacteria, bacteria solution was incubated with 70% isopropyl alcohol at room temperature for 1 hr) samples. Different volumes of live and dead bacteria solutions were mixed to generate a range of percent live solutions for calibration purposes. The sample results for bacteria killing ability were interpolated from the standard curve generated from calibration samples. Total bacteria concentration was determined by the measuring of the OD at 670 nm of the bacteria solution.

Zone of Inhibition Test

Antimicrobial performance was measured using a Zone of Inhibition test (ZOI) that was performed by the following method. Mueller-Hinton agar was prepared, sterilized and tempered in a water bath at 48-50°C. A suspension of bacteria in sterile phosphate-buffered water was prepared with approximately 10^8 CFU/ml. The agar was inoculated with the bacterial suspension to an approximate concentration of 10^5 CFU/ml (1:1000). The inoculated agar was swirled to mix and pipetted (~14 ml) into sterile Petri dishes (15 x 100 mm). The seeded agar was allowed to set for about 20 minutes to harden. An alcohol-disinfected die and cutting board were used to cut textile samples to desired size. Sterile forceps were used to place the samples onto the seeded,

hardened agar in center of plate. The plate was then placed into an incubator at 35-37°C for overnight (16-24 hours) incubation. After incubation the clear zones, no visible colonies formed, were measured in mm with calipers.

The zone of inhibition (ZOI) is then calculated by the following equation

ZOI = [diameter of clear zone (mm) – diameter of sample (mm)]/2

Saline Absorbency Test

Samples (2.54 cm by 2.54 cm) were soaked in saline. The samples were removed from the saline at various times and were lightly dabbed with a paper towel. The weight was recorded and the samples were placed back into the saline solution. The weight of saline absorbed per weight of dry coating was calculated as a function of swelling time in the saline using the following equation: (weight saline absorbed)/(dry coating sample weight) = [(saline swollen weight) – (dry sample weight)]/[(dry sample weight) – (weight of substrate)].

Peel Adhesion Test

Peel adhesion is measured as 180° peel from steel plates, at 23°C, 50%RH, 305 mm/min, 25mm wide using a Model 3M90 Slip/Peel tester (IMASS, Inc., Accord, MA). The samples were conditioned for 24 hours at controlled temperature and humidity. After conditioning the samples were adhered to a stainless steel panel using 2 kg roller and 4 passes. The samples were peeled from the stainless steel plate after 15 minutes of dwell time using a 0.305 meter/minute peel rate. Typically two 0.13 m long samples were measured and the average peel force recorded in ounces/inch (oz/in) and converted to Newtons per centimeter (N/cm).

Preparation of Examples

Examples 1-3 were prepared by first preparing a gel as described below and combining that with a lot of silver modified SALCARE that was prepared as outlined below.

Preparation of gel

Three lots of Styrene-isoprene-styrene (SIS) gel were prepared in the following manner. Lots 1 and used KRATON D4433-16 and Lot 3 used KRATON D1124 as the

SIS pellets. SIS pellets were gravimetrically fed into the feed throat (barrel 1) of a Werner Pfleiderer ZSK30 co-rotating twin-screw extruder (TSE) having a 30 mm diameter barrel and 15 barrel sections. Each temperature zone was a combination of two barrel sections (e.g., Zone 1 corresponded to barrel sections 2 and 3). Barrel section 1 was controlled at full cooling capacity for all SIS gel lots. A powdered antioxidant (IRGANOX 1010) was also gravimetrically fed into barrel section 1 for SIS gel lot 3. KAYDOL mineral oil was heated and added to the TSE as described in publication WO97/00163. The disclosed compounding process provides a method for making a gel by melting of the SIS elastomer followed by addition of the heated mineral oil. Heated mineral oil was sequentially injected into barrel sections 4, 6, 8, 10 and 12, respectively. The TSE screw speed for lots 1-3 was controlled to 400 rpm. The TSE temperature profile for lot 1 and 2 was controlled to 204°C, 204°C, 204°C, 191°C, 177°C, 149°C and 149°C for zones 1-7, respectively. The heated oil injections for lot 1 were controlled to 204°C, 204°C, 177°C, 149°C and 149°C respectively. The TSE temperature profile for lot 3 was controlled to 204°C, 227°C, 227°C, 204°C, 182°C, 171°C and 93°C for zones 1-7, respectively. The heated oil injections for lot 3 were controlled to 204°C, 204°C, 204°C, 177°C and 177°C respectively. Table 1 contains the material flow rates and Table 2 contains the compositional information for SIS gel lots 1-3.

Table 1. SIS gel lot flow rates

SIS Gel Lot#	SIS (g/min)	Barrel Section(S) and Oil addition # and Rate (g/min)					Total KAYDOL Oil (g/min)	IRGANOX 1010 (g/min)	Total Flow Rate (g/min)
		S4 Oil 1	S6 Oil 2	S8 Oil 3	S10 Oil 4	S12 Oil 5			
1	125	41	55	64	50	50	260	-	385
2	125	41	55	40	30	30	196	-	321
3	227	74	100	120	120	108	522	8	757

Table 2. SIS gel lots 1-2 compositions

SIS Gel Lot#	SIS Type	SIS (wt.%)	KAYDOL oil (wt.%)	IRGANOX 1010 (wt.%)	Total SIS Elastomer (wt.%)
1	linear	32.5	67.5	-	25.0
2	linear	39.0	61.0	-	30.0
3	radial	30.0	69.0	1.0	30.0

Preparation of the particles

Three lots of silver nitrate dispersed in SALCARE SC95 were prepared. Lot 1 was prepared by mixing 100 grams of SC95 with 2 milliliters (mls) of 5.6 molar (M) silver nitrate at a high speed using a 2 inch (5.08 cm) diameter, three-blade stainless steel paddle mixer. The silver nitrate solution was added drop wise such that all of the solution was added over ten minutes. After all of the silver nitrate solution was added the mixture was further mixed for another ten minutes. Sodium hydroxide solution (5.6M, 1.0 ml) was then added over 10 minutes and all the ingredients mixed for another 10 minutes. Lot 2 and 3 were prepared in a similar manner as Lot 1 except twice as much silver nitrate solution was added for Lot 3 and more sodium hydroxide was added, 1.8 ml for Lot 2 and 3.0 ml for Lot 3. Lot 3 was also dehydrated in a Ross mixer operating at 60°C, 11 hertz and 28 inches of mercury vacuum for 6 hours. Table 3 contains the compositional information for SALCARE SC95/$AgNO_3$ lots 1-3.

Table 3. SALCARE SC95/$AgNO_3$ lots 1-3 compositions

SALCARE SC95 Lot#	SALCARE SC95 (grams)	5.6M $AgNO_3$ (mls)	5.6M NaOH (mls)	DI H2O (wt.%)	$AgNO_3$/ NaOH Molar ratio
1	100.0	2.0	1.0	2.8	1/0.5
2	100.0	2.0	1.8	3.6	1/0.9
3	100.0	4.0	3.0	Dehydrated	1/0.75

Preparation of Examples 1-3

Examples 1-3 were prepared by combining pre-compounded SIS gel lots 1-3 with pre-compounded SALCARE SC95/$AgNO_3$ lots 1-3 in a Haake 25 mm diameter, fully intermeshing counter-rotating TSE. Example 1 was prepared by re-melting SIS gel lot 1 in a Bonnot extruder operating at 127°C. The molten gel was injected at 22.8 grams per minute into barrel section 1 of the TSE. SALCARE SC95 lot 1 was injected at ambient temperature into barrel section 3 at 15.2 grams per minute using a Zenith gear pump. The TSE was controlled at 300 rpm screw speed and 149°C temperature. The total material throughput was 38.0 grams per minute for all Examples. The SIS gel/SALCARE blend was discharged out of the TSE into a transport hose using a Zenith gear pump. The transport hose conveyed the molten gel blend to a 0.15 meter (m) wide single orifice film die. The transport hose and die were controlled to 157°C and 159°C, respectively. The molten gel blend was extruded into a nip formed by two polished steel rolls gapped at 0.25 mm and controlled to 106°C. A polyester (PET) knitted fabric (Lamports Filter Media, Inc, Cleveland, OH) having 0.8 mm by 0.7 mm (0.56 mm^2) rectangular open apertures, 0.20 mm thickness and 0.15 m width was fed into the nip at 1.4 m/min speed. As the fabric exited the molten gel blend/nip the article was cooled in air before being wound up with an inserted paper release liner. Upon cooling, a coated fabric having 78 g/m^2 coating weight and 0.75 mm by 0.6 mm (0.45 mm^2) rectangular open apertures was obtained. Examples 2 and 3 were prepared in the same manner only using Gel lot 2 and SALCARE Lot 2 for example 2 and Gel lot 3 and SALCARE Lot 3 for Example 3. Table 4 contains the process conditions and Table 5 contains the compositional information for Examples 1-3:

Table 4: Examples 1-3 process conditions

Ex.	SIS Gel Input (Barrel Section)	SALCARE Input (Barrel Section)	TSE Temp. (°C)	Transport Hose/Die Temp. (°C)	Steel Roll Temp. (°C)	Steel Roll Gap (mm)	Coating Speed (m/min)	Coating Weight (gr/m^2)
1	1	3	149	157/159	106	0.25	1.4	78
2	1	3	149	157/159	106	0.25	1.4	78
3	2	4	121	121	110	0.37	2.1	83

Table 5. Examples 1-3 compositions

Ex.	SIS gel Type (Lot #)	SIS (wt. %)	SALCARE SC95 Wt% (SALCARE Lot #)	KAYDOL oil (wt.%)	$AgNO_3$ (wt.%)	NaOH (wt.%)	DI H2O (wt.%)
1	Linear (1)	15.0	38.0 (1)	45.0	0.8	0.08	1.12
2	Linear (2)	18.0	37.6 (2)	42.0	0.8	0.16	1.44
3*	Radial (3)	18.0	38.2 (3)	41.4	1.6	0.24	-

* Example 3 also contains IRGANOX 1010 at 0.6 wt%.

Preparation of Example 4

Example 4 was prepared by soaking Example 1 in the aqueous silver (I) oxide solution for two minutes. The soaked film was then placed in an oven operating at 100°C for 30 minutes.

Testing of Example 3 Adhesion

Example 3 (the gel coated PET fabric) and slabs (1 mm thick) having the composition of Example 3 were tested for 180° peel adhesion from stainless steel using the peel adhesion test. Measurements of the instantaneous peel force was measured for two 0.13 m long samples and averaged. The 180° peel adhesion from stainless steel was 0.0 N/cm for both the slab and gel coated PET fabric of Example 3. The extremely low 180° peel adhesion demonstrate the inability of the composition and articles of the invention to form a strong adhesive bond. These low values, for the composition and article, are considered to be non-adhesive or non-adherent.

Testing of Examples 1-3 Absorbency

Examples 1-3 were tested for their ability to absorb 0.8 wt.% NaCl (saline) as outlined in the Saline Absorbency test. Table 6 contains the amount of saline absorbed as a function of time.

Table 6. Saline absorbency vs. time for Examples 1-3

Ex.	SIS gel Type (Lot #)	SIS (wt.%)	SALCARE Type (Lot #)	0.5 hour Saline Absorb.	1 hour Saline Absorb.	2 hours Saline Absorb.	6 hours Saline Absorb.	24 hours Saline Absorb.
1	Linear (1)	15.0	SC95 (1)	0.9	1.7	1.5	1.6	1.8
2	Linear (2)	18.0	SC95 (2)	2.9	2.9	3.1	2.0	2.2
3	Radial (3)	18.0	SC95 (3)	2.4	2.8	2.8	nm	nm

nm- not measured

The saline absorbency data demonstrates that the composition and article of the invention can absorb an amount of saline that is 1-3 times their dry weight. All samples remained intact after saline exposure.

Optical micrographs of Example 1 before and after 2 hours of saline exposure were obtained at 2.5x magnification in reflection mode and analyzed for the size of the aperature by measurements of the resulting micrographs. The aperature area was 0.45 mm2 as coated and 0.35 mm2 in the equilibrium saline hydrated state for Example 1.

Testing of Examples-Antimicrobial performance

Example 3 was tested for antimicrobial performance against *Staph. Aureus* using the Zone of Inhibition Test. Example 3 was sterilized using a cobalt-γ source at both 25 and 40 kilograys (kGy). The samples were tested in the dry state. All samples had a diameter of 24 mm. Table 7 contains the results from the Zone of Inhibition Test for Example 3 at two sterilization exposure levels and a commercially available silver dressing, Example 5 (Comparative-ACTICOAT available from Smith and Nephew, Largo, Florida).

Table 7. Zone of inhibition test results for Examples 3 and 5

Example	SIS (wt.%)	SALCARE Type (wt.%)	KAYDOL oil (wt.%)	$AgNO_3$ (wt.%)	NaOH (wt%)	20 kGy ZOI (mm)	40 kGy ZOI (mm)	Ave. ZOI (mm)
3	18.0	SC95 (38.2)	41.4	1.6	0.24	3.4	3.8	3.6
5 (Comp)	-	-	-	-		-	-	3.3

The silver containing dressings of Example 3 has a higher measured ZOI than the Example 5, the commercially available dressing. The relative amount of total silver in a one square inch portion of dressing is 0.9 milligrams (mg) of $AgNO_3$ (0.6 mg Ag^+) in Example 3, calculated from the known material input amounts and coating weight, and 2.9 mg total silver (1.3 mg ammonia soluble silver – the "active" form) for the Example 5(Wounds 10(6), 179-188, 1988 Health Management Publications). Example 3 dressing has significantly less silver, either total or active form and stills performs better in the ZOI test than the comparative example.

Examples 1, 2 and 4 were tested using the % Live Bacteria Test. Samples having a diameter of 0.125 inches (3.2 mm) were placed in contact with 7 mls of bacterial solution having approximately 10^8 counts of bacteria. Table 8 contains the results of the % Live Bacteria Test at 2 hours of contact of Examples 1,2 and 4 with the bacterial solution.

Table 8. Results from %Live Bacteria Test for Dressings

Ex.#	Example Description	% Live 2 hrs
1	SIS gel- $AgNO_3$/NaOH Molar Ratio 1/0.5	17.5
2	SIS gel- $AgNO_3$/NaOH Molar Ratio 1/0.9	12.9
4	Ex. 1 treated with Ag_2O solution	1.1
	Bacteria only	97.0

Preparation of Examples 6-10

Comparative Example 6 was prepared by mixing 100 grams of a cationic dispersion (SALCARE SC95) with 4 milliliters (mL) of 5.6M $AgNO_3$ at approximately 1000 rpm using a 5.08 cm diameter, three-blade stainless steel paddle that was powered by an air-drive. The 5.6M $AgNO_3$ was added drop-wise over 10 minutes. The emulsion was mixed for an additional 10 minutes and subsequently vacuum dried at 60°C and a pressure of 50.8 of mercury for 5 hours. Example 7 was prepared in the same manner as Comparative Example 6 except that 3 mL of 5.6M NaOH were added drop-wise over 10 minutes after the 5.6M $AgNO_3$ was added. Example 8 was prepared in the same manner as Example 7 except that an anionic dispersion (SALCARE SC91) was used in place of the cationic dispersion (SALCARE SC95) and the solution was exposed to an air convection oven at 130°C for 30 minutes instead of evacuating the DI water under temperature and vacuum. Example 9 was prepared in the same manner as Example 8 except that 4 mL of 5.6M $AgNO_3$ and 4 mL of 5.6M NaOH were added to the dispersion. Example 10 was prepared in the same manner as Example 8 except that 3.9 mL of 10 wt.% H_2O_2 was added to the blend before air convection oven exposure. Table 9 contains the compositional information for Comparative Example 6 and Examples 7-10.

Table 9. Composition of Examples 6-10

Ex.	SALCARE SC95 (wt.%)	SALCARE SC91 (wt.%)	$AgNO_3$ (wt.%)	NaOH (wt.%)	H_2O_2 (wt.%)	DI H2O (wt.%)	Final Treatment
6(Comparative)	96.3	-	3.7	-	-	-	60°C, 0.7 atm (5 hrs)
7	95.5	-	3.6	0.9	-	-	60°C, 0.7 atm (5 hrs)
8	-	94.0	1.8	0.4	-	3.8	130°C (0.5 hrs)
9	-	88.7	3.4	0.8	-	7.1	130°C (0.5 hrs)
10	-	90.4	1.7	0.4	0.4	7.1	130°C (0.5 hrs)

Comparative Example 6 and Examples 7-10 were tested for antimicrobial activity against *Staph. aureas* using the % Live Bacteria Test. One drop of the Example dispersions was dripped into the bacterial solution and mixed. The % live

bacteria at 2 hours was measured. All bacterial solution volumes were 7 mL. The initial live bacteria concentration was 1.0×10^8 bacteria/mL. The results are tabulated in Table 10.

Table 10. Results from %Live Bacteria Test

Example	Sample Weight (g)	% Live after 2 hours
6(Comparative)	0.017	27.9
7	0.030	1.7
8	0.014	5.8
9	0.019	0.7
10	0.016	4.5

WHAT IS CLAIMED IS:

1. A polymer composition comprising:

a hydrophilic polymer; and

a bioactive agent selected from the group consisting of a metal oxide of silver, copper, zinc, and combinations thereof;

wherein the bioactive agent is dispersed within the hydrophilic polymer; and

wherein substantially all of the bioactive agent has a particle size less than one micron.

2. The polymer composition of claim 1, wherein the hydrophilic polymer is an anionic polymer, a cationic polymer, an amphoteric polymer, and combinations thereof.

3. The polymer composition of claim 1 wherein the hydrophilic polymer is selected from the group consisting of a polyhydroxyalkyl acrylates and methacrylates; poly(meth)acrylic acid and salts thereof; polyvinyl alcohols; polyoxyalkylenes; polystyrene sulfonates; polysaccarides; alginates; gums; cellulosics; polymers prepared from water-soluble hydrazine derivatives; polyurethanes, mono-olefinic sulfonic acids and their salts; and combinations thereof.

4. The polymer composition of claim 1 wherein the hydrophilic polymer is an amine-containing organic polymer selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof.

5. The polymer composition of claim 1 wherein the hydrophilic polymer is a quaternary ammonium salt of an organic polymer.

6. The polymer composition of claim 1, wherein the hydrophilic polymer is a carboxylic acid-containing organic polymer.

7. A polymer composition preparable by a method comprising combining components comprising:

a hydrophilic polymer;

a metal compound selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility of at least 0.1 gram per liter in water; and

a hydroxide source that converts the metal compound to the corresponding metal oxide;

wherein the components are combined in a manner to disperse the metal oxide within the hydrophilic polymer.

8. The polymer composition of claim 7 wherein the hydrophilic polymer is selected from the group consisting of polyhydroxyalkyl acrylates and methacrylates; poly(meth)acrylic acid and salts thereof; polyvinyl alcohols; polyoxyalkylenes; polystyrene sulfonates; polysaccarides; alginates; gums; cellulosics; polymers prepared from water-soluble hydrazine derivatives; polyurethanes, mono-olefinic sulfonic acids and their salts; and combinations thereof.

9. The polymer composition of claim 7 wherein the hydrophilic polymer is an amine-containing organic polymer selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof.

10. The polymer composition of claim 9 wherein the amine-containing organic polymer is a quaternary ammonium salt of an organic polymer.

11. The polymer composition of claim 7 wherein the composition includes water in an amount of 1 to 20 wt%, based on the total weight of the hydrophilic polymer composition.

12. The polymer composition of claim 7, wherein the hydrophilic polymer is a carboxylic acid-containing organic polymer.

13. A polymer composition preparable by a method comprising combining components comprising:

a hydrophilic polymer;

an ammonia source;

a metal oxide selected from the group consisting of silver oxides, copper oxides, zinc oxide, and combinations thereof;

wherein the components are combined in a manner to disperse the metal oxide within the hydrophilic polymer; and

wherein the metal oxide particle size is less than one micron.

14. The polymer composition of claim 13 wherein the hydrophilic polymer is selected from the group consisting of polyhydroxyalkyl acrylates and methacrylates; poly(meth)acrylic acid and salts thereof; polyvinyl alcohols; polyoxyalkylenes; polystyrene sulfonates; polysaccarides; alginates; gums; cellulosics; polymers prepared from water-soluble hydrazine derivatives; polyurethanes, mono-olefinic sulfonic acids and their salts; and combinations thereof.

15. The polymer composition of claim 13 wherein the ammonia source is selected from the group consisting of ammonia and ammonium salts.

16. The polymer composition of claim 15 wherein the ammonium salt is selected from the group consisting of ammonium pentaborate, ammonium acetate, ammonium carbonate, ammonium peroxyborate, ammonium tertraborate, triammonium citrate, ammonium carbamate, ammonium bicarbonate, ammonium malate, ammonium nitrate, ammonium nitrite, ammonium succinate, ammonium sulfate, ammonium tartarate, and mixtures thereof.

17. The polymer composition of claim 13 wherein the ammonia source and metal oxide form an ammonia-metal complex with a solubility greater than 0.1 gram per liter in water.

18. The polymer composition of claim 13, wherein the hydrophilic polymer is a carboxylic acid-containing organic polymer.

19. A composition preparable by a method comprising combining components comprising:

a dispersion comprising absorbent hydrophilic microparticles, wherein the microparticles when in a substantially nonhydrated form have an average particle size of 10 microns or less;

a metal compound selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water; and

a hydroxide source that converts the metal compound to the corresponding metal oxide;

wherein the components are combined in a manner to produce a polymer composition wherein the metal oxide is incorporated within the microparticles.

20. The polymer composition of claim 19 wherein the dispersion comprises absorbent hydrophilic microparticles, wherein the microparticles comprise an amine-containing organic polymer selected from the group consisting of a poly(quaternary amine), a polylactam, a polyamide, and combinations thereof.

21. The polymer composition of claim 19 wherein the dispersion comprises absorbent hydrophilic microparticles, wherein the microparticles comprise a carboxylic –acid containing organic polymer.

22. The polymer composition of claim 19 wherein the microparticles have an average particle size of 1 micron or less when in a substantially nonhydrated form.

23. The polymer composition of claim 19 wherein the microparticles have an average particle size of 0.5 micron or more when in a substantially nonhydrated form.

24. The polymer composition of claim 19 further comprising secondary absorbent particles having an average particle size of greater than 10 microns when in a substantially nonhydrated form.

25. The polymer composition of claim 24 wherein the secondary absorbent particles having an average particle size of greater than 10 microns are superabsorbent.

26. The polymer composition of claim 19 wherein the microparticles are superabsorbent.

27. A polymer composition preparable by a method comprising combining components comprising:

an organic polymer matrix;

a dispersion comprising absorbent hydrophilic microparticles, wherein the microparticles when in a substantially nonhydrated form have an average particle size of 10 microns or less;

a metal compound selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility of at least 0.1 gram per liter in water; and

a hydroxide source that converts the metal compound to the corresponding metal oxide;

wherein the components are combined in a manner to produce a polymer composition wherein the metal oxide is incorporated within the microparticles.

28. The polymer composition of claim 27 wherein the dispersion comprises absorbent hydrophilic microparticles, wherein the microparticles comprise an amine-containing organic polymer selected from the group consisting of a poly(quaternary amine), a polylactam, a polyamide, and combinations thereof.

29. The polymer composition of claim 27 wherein the dispersion comprises absorbent hydrophilic microparticles, wherein the microparticles comprise a carboxylic-acid-containing organic polymer.

30. The polymer composition of claim 27 wherein the microparticles have an average particle size of 1 micron or less when in a substantially nonhydrated form.

31. The polymer composition of claim 27 wherein the microparticles have an average particle size of 0.5 micron or more when in a substantially nonhydrated form.

32. The polymer composition of claim 27 further comprising secondary absorbent particles having an average particle size of greater than 10 microns when in a substantially nonhydrated form.

33. The polymer composition of claim 32 wherein the secondary absorbent particles having an average particle size of greater than 10 microns are superabsorbent.

34. The polymer composition of claim 27 wherein the microparticles are superabsorbent.

35. The polymer composition of claim 27 wherein the organic polymer matrix comprises an elastomeric polymer.

36. The polymer composition of claim 35 wherein the elastomeric polymer is selected from the group consisting of a polyisoprene, a styrene-diene block copolymer, a natural rubber, a polyurethane, a polyether-block-amide, a poly-alpha-olefin, a (C1-C20) acrylic ester of meth(acrylic) acid, an ethylene-octene copolymer, and combinations thereof.

37. The polymer composition of claim 27 wherein the organic polymer matrix comprises a thermoplastic polymer.

38. The polymer composition of claim 37 wherein the thermoplastic polymer is a polyolefin.

39. The polymer composition of claim 27 wherein the organic polymer matrix comprises a hydrophilic polymer selected from the group consisting of a polysaccharide, a polyether, a polyurethane, a polyacrylate, a cellulosic, and an alginate.

40. The polymer composition of claim 27 wherein the hydrophilic polymer microparticles comprise a quaternary ammonium salt of an organic polymer.

41. The polymer composition of claim 40 wherein the microparticles comprise a cationic homopolymer of the methyl chloride quaternary salt of 2-(dimethylamino)ethyl methacrylate.

42. The polymer composition of claim 27 further comprising an additive selected from the group consisting of a plasticizer, a tackifier, a crosslinking agent, a stabilizer, an extruding aid, a filler, a pigment, a dye, a swelling agent, a foaming agent, a chain transfer agent, and combinations thereof.

43. The polymer composition of claim 27 wherein the organic polymer matrix comprises a mixture of two or more polymers.

44. The polymer composition of claim 27 wherein the microparticles are present in an amount of 1 wt-% to 60 wt-%, based on the total weight of the polymer composition.

45. The polymer composition of claim 27 wherein the composition includes water in an amount of 1 wt-% to 20 wt-%, based on the total weight of the polymer composition.

46. The polymer composition of claim 1 in the form of an extruded film.

47. The polymer composition of claim 1 in the form of a foam.

48. The polymer composition of claim 1 wherein the composition is stable.

49. The polymer composition of claim 1, wherein the composition is in the form of a hydrocolloid.

50. The polymer composition of claim 7 comprising water in an amount of less than 1 weight percent, based on the total weight of the polymer composition.

51. The polymer composition of claim 27 wherein the hydrophobic material forms a discontinuous phase and the hydrophilic polymer forms a continuous phase.

52. The polymer composition of claim 27 wherein the hydrophilic polymer forms a discontinuous phase and the hydrophobic material forms a continuous matrix.

53. The polymer composition of claim 52 wherein the hydrophobic material is liquid at room temperature.

54. The polymer composition of claim 53 wherein the hydrophobic material is mineral oil.

55. The polymer composition of claim 52 wherein the hydrophobic material is solid at room temperature.

56. The polymer composition of claim 52 wherein the hydrophobic material comprises an elastomeric polymer.

57. The polymer composition of claim 56 wherein the elastomeric polymer is selected from the group consisting of a polyisoprene, a styrene-diene block copolymer, a natural rubber, a polyurethane, a polyether-block-amide, a poly-alpha-olefin, a (C1-C20) acrylic esters of meth(acrylic) acid, an ethylene-octene copolymer, and combinations thereof.

58. The polymer composition of claim 56 wherein the elastomeric polymer is selected from the group consisting of styrene-isoprene-styrene (SIS), styrene-butadiene-styrene (SBS), styrene-ethylene-propylene-styrene (SEPS), and styrene-ethylene-butylene-styrene (SEBS).

59. The polymer composition of claim 7 further comprising a swelling agent.

60. A medical article comprising the polymer composition of claim 1.

61. A method of using a polymer composition comprising applying the polymer composition of claim 1 to a wound.

62. A method of making a polymer composition, wherein the method comprises:

combining a dispersion comprising hydrophilic organic microparticles with water and a metal compound under conditions effective to distribute substantially all of the metal compound in the hydrophilic organic microparticles, wherein the metal compound is selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof; wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water;

adding a hydroxide source to convert the metal compound to the corresponding metal oxide;

optionally adding a secondary organic polymer to the dispersion; and

optionally removing a substantial portion of the water.

63. The method of claim 62, further comprising the step of adding an oxidizing agent to form a higher valence metal oxide.

64. The method of claim 62, further comprising subjecting the polymer composition to radiation.

65. The method of claim 62, further comprising extruding or molding the composition.

66. A method of making a polymer composition, wherein the method comprises:

combining monomers for a hydrophilic organic polymer with a metal compound under conditions effective to polymerize the monomers and distribute substantially all of the metal compound within the hydrophilic organic polymer, wherein the metal compound is selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof; wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water;

adding a hydroxide source to convert the bioactive agent to the corresponding metal oxide; and

optionally adding a secondary organic polymer to the hydrophilic organic polymer.

67. A wound dressing comprising the composition of claim 27 coated on an apertured liquid permeable substrate wherein the composition is nonadherent.

68. A medical article comprising a substrate impregnated with one or more metal oxides of silver, copper and zinc wherein the impregnated substrate has less than 1 N/cm peel strength to steel and does not adhere to wound tissue.

69. A medical article comprising a substrate impregnated with one or more metal oxides of silver, copper and zinc with an average particle size less than 1 micron dispersed within a hydrocolloid.

70. A method of forming silver oxide in a hydrocolloid, the method comprising:

providing a mixture of a hydrocolloid and a solution of the silver compound with a solubility of at least 0.1 gram per liter in water;

adding a hydroxide source to form an metal oxide of silver (I);

wherein the silver oxide is dispersed within the hydrocolloid.

71. The method of claim 70, further comprising the step of adding an oxidizing agent to form a higher valence oxide of silver.

72. The method of claim 70, further comprising the step of adding a hydrophobic polymer.

73. The medical article of claim 70 wherein the hydrocolloid has a particle size less than 10 microns.

74. The medical article of claim 72 wherein the hydrophobic polymer comprises styrene-isoprene-styrene.

75. A polymer composition comprising:

a hydrophilic polymer; and

a silver oxide;

wherein the silver oxide is dispersed within the hydrophilic polymer; and

wherein substantially all of the silver oxide has a average particle size less than one micron.

76. A method of making a polymer composition comprising:

combining a hydrophilic polymer,

a metal compound selected from the group consisting of a silver compound, a copper compound, a zinc compound, and combinations thereof, wherein the silver compound has a solubility in water of at least 0.1 gram per liter in water; and

a hydroxide source that converts the metal compound to the corresponding metal oxide; and

dispersing the metal oxide within the hydrophilic polymer.

77. The method of claim 76 wherein the hydrophilic polymer is selected from the group consisting of polyhydroxyalkyl acrylates and methacrylates; poly(meth)acrylic acid and salts thereof; polyvinyl alcohols; polyoxyalkylenes; polystyrene sulfonates; polysaccarides; alginates; gums; cellulosics; polymers prepared from water-soluble hydrazine derivatives; polyurethanes, mono-olefinic sulfonic acids and their salts; and combinations thereof.

78. The method of claim 76 wherein the hydrophilic polymer is an amine-containing organic polymer selected from the group consisting of poly(quaternary amines), polylactams, polyamides, and combinations thereof.

79. The method of claim 78 wherein the amine-containing organic polymer is a quaternary ammonium salt of an organic polymer.

80. The method of claim 76 wherein the hydrophilic polymer comprises absorbent hydrophilic microparticles, wherein the microparticles comprise a carboxylic–acid containing organic polymer.

81. The method of claim 76, wherein the hydroxide source is added after combining the bioactive agent and the hydrophilic polymer.

82. The method of claim 76, further comprising combining an oxidizing agent with the hydrophilic polymer, the bioactive agent, and the hydroxide source.

83. The method of claim 82, wherein the oxidizing agent is added after combining the hydrophilic polymer, the bioactive agent, and the hydroxide source.

84. A method of making a polymer composition, comprising:

combining a hydrophilic polymer;

an ammonia source; and

a metal oxide selected from the group consisting of silver oxides, copper oxides, zinc oxides, and combinations thereof; and

dispersing the metal oxide within the hydrophilic polymer;

wherein the metal oxide particle size is less than one micron.

85. The method of claim 84, wherein the ammonia source and metal oxide are combined before combining with the hydrophilic polymer.

86. The method of claim 84, further comprising combining an oxidizing agent with the hydrophilic polymer, the ammonia source, and the metal oxide.

87. The method of claim 86, wherein the oxidizing agent is added after combining the hydrophilic polymer, the ammonia source, and the metal oxide.

88. The method of claim 84, further comprising combining the components in the presence of water and removing a substantial portion of the water.

89. A medical article comprising the polymer composition of claim 7.

90. A method of using a polymer composition comprising applying the polymer composition of claim 7 to a wound.

91. A medical article comprising the polymer composition of claim 13.

92. A method of using a polymer composition comprising applying the polymer composition of claim 13 to a wound.

93. A wound dressing comprising the composition of claim 13 coated on an apertured liquid permeable substrate wherein the composition is nonadherent.

INTERNATIONAL SEARCH REPORT

PCT/US2004/040706

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L26/00 A61L15/22 A61L15/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 91/09633 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 11 July 1991 (1991-07-11) page 22, line 35 - page 23, line 29 page 25, line 26 claim 1-14, especially claim 8	1-6, 46-50, 60,61,75
Y	US 2001/010016 A1 (MODAK SHANTA ET AL) 26 July 2001 (2001-07-26) '0023!, '0024!, '0049!, '0065!-'0070! claims 8,18,22-24,32-34	1-6, 46-50, 60,61,75

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 6 582 711 B1 (ASMUS ROBERT A ET AL) 24 June 2003 (2003-06-24) claims 1-25 example 9 column 10, line 45 - line 64	1-6, 46-50, 60,61,75
Y	US 2 521 713 A (GOETZ ALEXANDER) 12 September 1950 (1950-09-12) column 11, line 27 - line 45	1-6, 46-50, 60,61,75
Y	US 4 603 152 A (LAURIN ET AL) 29 July 1986 (1986-07-29) abstract column 2, line 48 - column 3, line 27 examples 1-4,10-15 claims 1-5	1-6, 46-50, 60,61,75
Y,P	WO 2004/080499 A (3M INNOVATIVE PROPERTIES COMPANY; BURTON, SCOTT, A; HYDE, PATRICK, D) 23 September 2004 (2004-09-23) page 8, line 30 - page 9, line 12 claims 1-73	1-6, 46-50, 60,61,75

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Designation: D 2857 – 93

An American National Standard

Standard Practice for Dilute Solution Viscosity of Polymers[1]

This standard is issued under the fixed designation D 2857; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This practice covers the determination of the dilute solution viscosity of polymers. There are several ASTM standards (Test Methods D 789, D 1243, D 1601, and D 4603, and Practice D 3591) that describe dilute solution viscosity procedures for specific polymers, such as nylon, poly(vinyl chloride), polyethylene, and poly(ethylene terephthalate). This practice is written to augment these standards when problems arise with which the specific procedure is not concerned, or when no standard is available for the polymer under investigation.

1.2 This practice is applicable to all polymers that dissolve completely without chemical reaction or degradation to form solutions that are stable with time at a temperature between ambient and 150°C. Results are usually expressed as relative viscosity (viscosity ratio), inherent viscosity (logarithmic viscosity number), or intrinsic viscosity (limiting viscosity number) (see 3.1).

1.3 For polyamides, relative viscosity values by this procedure are not equivalent to those determined by Test Methods D 789.

1.4 *This standard does not purport to address all of the safety problems, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

NOTE 1—This standard and ISO 1628, "Plastics—Determination of Viscosity Number and Limiting Viscosity Number," are technically equivalent.

2. Referenced Documents

2.1 *ASTM Standards:*

D 445 Test Method for Kinematic Viscosity of Transparent and Opaque Liquids (and the Calculation of Dynamic Viscosity)[2]

D 446 Specification for Operating Instructions for Glass Capillary Kinematic Viscometers[2]

D 789 Test Methods for Determination of Relative Viscosity, Melting Point, and Moisture Content of Polyamide (PA)[3]

D 883 Terminology Relating to Plastics[3]

D 1243 Test Method for Dilute Solution Viscosity of Vinyl Chloride Polymers[3]

D 1600 Terminology for Abbreviated Terms Related to Plastics[3]

D 1601 Test Method for Dilute Solution Viscosity of Ethylene Polymers[3]

D 3591 Practice for Determining Logarithmic Viscosity Number of Poly(Vinyl Chloride) (PVC) in Formulated Compounds[4]

D 4603 Test Method for Determining Inherent Viscosity of Poly(Ethylene Terephthalate) (PET)[5]

D 5226 Practice for Dissolving Polymer Materials[5]

E 1 Specification for ASTM Thermometers[6]

2.2 *ISO Standard:*

1628/1 Guidelines for the Standardization of Methods for the Determination of Viscosity Number and Limiting Viscosity Number of Polymers in Dilute Solution[7]

2.3 *National Institute of Standards and Technology Document:*

Circular No. C602 Testing of Glass Volumetric Apparatus[8]

3. Terminology

3.1 *Definitions*—Terms and definitions in Terminology D 883 and abbreviations in Terminology D 1600 are applicable to this practice. The following definitions[9] are applicable to this practice.

3.1.1 *inherent viscosity, η_{inh}, n*—the ratio of the natural logarithm of the relative viscosity to the mass concentration of the polymer, *c*: $\eta_{inh} = (\ln \eta_r)/c$.

3.1.1.1 *Discussion*—Also known as the logarithmic viscosity number, η_{ln}. See also 3.1.3.2.

3.1.2 *intrinsic viscosity, $[\eta]$, n*—the limiting value of the reduced viscosity or the inherent viscosity at infinite dilution of the polymer: $[\eta] = \lim_{c \to 0} (\eta_i/c) = \lim_{c \to 0} \eta_{inh}$.

3.1.2.1 *Discussion*—Also known as the limiting viscosity number and in the literature as the Staudinger index. See also 3.1.3.2.

3.1.3 *reduced viscosity, n*—the ratio of the relative viscosity increment to the mass concentration of the polymer, *c*, that is, η_i/c.

3.1.3.1 *Discussion*—Also known as the viscosity number. The unit must be specified; cm^3/g is recommended.

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[1] This practice is under the jurisdiction of ASTM Committee D-20 on Plastics and is the direct responsibility of Subcommittee D20.70 on Analytical Methods.

Current edition approved Oct. 15, 1993. Published December 1993. Originally published as D 2857 – 70. Last previous edition D 2857 – 87.

[2] *Annual Book of ASTM Standards*, Vol 05.01.

[3] *Annual Book of ASTM Standards*, Vol 08.01.

[4] *Annual Book of ASTM Standards*, Vol 08.02.

[5] *Annual Book of ASTM Standards*, Vol 08.03.

[6] *Annual Book of ASTM Standards*, Vol 14.03.

[7] Available from American National Standards Institute, 11 W. 42nd St., 13th Floor, New York, NY 10036.

[8] Available from National Institute of Standards and Technology, U.S. Department of Commerce, Washington, DC 20234.

[9] International Union of Pure and Applied Chemistry, *Compendium of Macromolecular Nomenclature*, Blackwell Scientific Publications, Oxford, England, 1991.

3.1.3.2 *Discussion*—This quantity and those defined in 3.1.1 and 3.1.2 are neither viscosities nor pure numbers. The terms are to be looked upon as traditional names. Any replacement by consistent terminology would produce unnecessary confusion in the polymer literature.

3.1.4 *relative viscosity, η_r, n*—the ratio of the viscosity of the solution, η, to the viscosity of the solvent, η_s, that is, $\eta_r = \eta/\eta_s$.

3.1.4.1 *Discussion*—Also known as the viscosity ratio.

3.1.5 *relative viscosity increment, η_i, n*—the ratio of the difference between the viscosities of solution and solvent to the viscosity of the solvent, that is, $\eta_i = (\eta - \eta_s)/\eta_s$.

3.1.5.1 *Discussion*—The use of the term specific viscosity for this quantity is discouraged, since the relative viscosity increment does not have the attributes of a specific quantity.

4. Summary of Practice

4.1 General procedures are given for the determination of the dilute solution viscosity of polymers, including descriptions of apparatus, reagents and materials, and sample preparation, as well as measurement procedures and calculations.

4.2 If detailed test methods are available for the polymers of interest, such as those mentioned in 1.1, this practice provides information of a general nature to augment the detailed treatments in the relevant test methods.

5. Significance and Use

5.1 The determination of dilute solution viscosity provides one item of information towards the molecular characterization of polymers. When viscosity data are used in conjunction with other molecular parameters, the properties of polymers depending on their molecular structure may be predicted.

5.2 Viscosity is dependent on molecular weight distribution, so with certain restrictions, satisfactory correlations can be obtained between dilute-solution viscosity and molecular parameters such as molecular weight or chain length. The most limiting restrictions that must be observed are as follows:

5.2.1 It must be known that the polymers used to establish the correlations and those to which they are applied do not consist of or contain branched species. Basically a measure of molecular size and not molecular weight, the dilute solution viscosity can be correlated appropriately with molecular weight or chain length only if there is a unique relationship between the mass and the size of the dissolved polymer molecules. This is the case for linear, but not for most branched, polymers.

5.2.2 For reasons similar to those outlined in 5.2.1, it must be required that the polymers to which the correlations are applied have the same chemical composition as those used in establishing the relationships.

5.3 For polymers meeting the restrictions of 5.2, empirical relationships can be developed between the dilute solution viscosity of a polymer and its hydrodynamic volume or average chain dimension (radius of gyration or end-to-end distance). Such relationships depend upon any variables influencing this molecular size of the dissolved polymer. The most important of these variables are solvent type and temperature. Thus, the solution viscosity of a given polymer specimen depends on the choice of these variables, and they must always be specified with the viscosity for complete identification.

5.4 The solution viscosity of a polymer of sufficiently high molecular weight may depend on rate of shear in the viscometer, and the viscosity of a polyelectrolyte (polymer containing ionizable chemical groupings) will depend on the composition and ionic strength of the solvent. Special precautions beyond the scope of this practice are required when measuring such polymers.

5.5 Finally, the viscosity of polymer solutions may be affected drastically by the presence of recognized or unrecognized additives in the sample, including but not limited to colorants, fillers, or low-molecular-weight species.

6. Apparatus

6.1 *Volumetric Flasks,*[10] 100-mL or other size found convenient.

6.2 *Transfer Pipets,*[10] sizes between 1 and 25 mL, as required. Transfer pipets for use with polymer solutions should have about 2 mm cut from their lower tips to permit more rapid transfer of the solution to the viscometer.

6.3 *Constant-Temperature Bath,* capable of maintaining ±0.01°C at the desired temperature (usually between 25 and 150°C). Less stringent temperature control (±0.02°C) is satisfactory upon demonstration that the precision of results is not affected.

6.4 *Viscometer,* glass capillary type, as described in Specification D 446. Efflux time for the solvent and temperature used shall be greater than 200 s (except that efflux time for semi-micro viscometers shall be greater than 80 s), to eliminate the need for kinetic energy corrections.

6.4.1 Two types of viscometers are commonly used: One is a constant-volume device of simple construction, recommended for use where solution viscosity is to be measured at a single concentration, as for determination of the reduced viscosity (viscosity number) or inherent viscosity (logarithmic viscosity number). It may also serve for the determination of the intrinsic viscosity (limiting viscosity number) through measurement of several solutions having different concentrations.

6.4.2 The second type viscometer, commonly called a dilution viscometer, is a time-saving device for the determination of intrinsic viscosity (limiting viscosity number) since it does not require constant liquid volume for operation. Several concentrations of a polymer solution can be tested by adding a known quantity of the solvent at the test temperature directly to the viscometer, mixing, measuring the viscosity, and then making the next dilution. The viscosity of the pure solvent must be measured separately.

6.4.3 An alternative procedure is to start with the minimum volume of the pure solvent, then add aliquots of a concentrated stock solution to the viscometer to obtain values of the relative viscosity (viscosity ratio) at successively higher concentrations. The choice of procedures is dictated by the range of volumes with which the viscometer will operate and the range of concentrations desired for test.

[10] Glassware should conform to the standards of accuracy in National Institute of Standards and Technology Circular No. C602.

6.5 *Timer,* graduated in divisions of 0.1 s or less, as described in Test Method D 445.

6.6 *Thermometer,* suitable for the specified test temperature and conforming to the specifications of Specification E 1, Kinematic Viscosity Thermometers ASTM 110C (for use at 135°C) and 118C (for use at 30°C).

6.7 *Fritted Glass Filter Funnel,* coarse grade,[11] or equivalent.

7. Reagents and Materials

7.1 *Solvents,* as required, or as recommended in Appendix X1.

7.2 *Heat Transfer Liquid,* for constant temperature bath.

NOTE 2—The following materials have been used as heat-transfer liquids: (*1*) silicone oil,[12] (*2*) mineral oil, (*3*) peanut oil, (*4*) water, and (*5*) water-miscible liquid, such as glycerin or ethylene glycol. The material selected must not discolor or smoke on prolonged exposure at the test temperature; in some cases discoloring may be inhibited by the use of an antioxidant. The use of water or a water-miscible liquid facilitates cleaning glassware used in the test.

7.3 *Nitrogen,* for purging.

8. Sample Preparation

8.1 Do not predry or condition the sample unless the material is known to be hygroscopic.

8.2 If it is known that the sample dissolves only slowly in the selected solvent, pretreating the sample to reduce its particle size may be advisable.

NOTE 3—Some samples can be pulverized conveniently in a rotary cutting mill with a 20-mesh screen at the outlet of its pulverizing chamber.[13]

NOTE 4—**Caution:** Take care to avoid overheating the sample during pulverization, which might lead to thermal degradation. Low-melting polymers, or hard, tough samples, often can be satisfactorily pulverized only at very low temperature as provided by dry ice or liquid nitrogen.

9. Procedure

9.1 Weigh an appropriate sample into a tared 100-mL volumetric flask (or weigh and transfer quantitatively to the flask). If the sample is known to oxidize easily in the subsequent dissolution step, the flask may be purged with nitrogen.

NOTE 5—Solution concentrations for some common polymers are recommended in Appendix X1. Since other sizes of volumetric flasks may be used, depending on the viscometer size and the amount of sample available, adjust sample weights and the solvent and solution volumes accordingly.

NOTE 6—For greater reliability of results, select the sample size on the basis of experiment to give a relative viscosity (viscosity ratio) near 1.5. If several concentrations of a solution of a single sample are to be used (Note 8), select them so that the relative viscosity (viscosity ratio) falls in the range from 1.2 to 2.0.

NOTE 7—Preparation of a single solution may often suffice, either for determining the relative viscosity (viscosity ratio) or inherent viscosity (logarithmic viscosity number), or as a stock solution for use in a dilution viscometer to determine the intrinsic viscosity (limiting viscosity number). If more than one solution concentration is desired, weigh a series of specimens (often four) into separate flasks, selecting specimen weights to give the desired solution concentration.

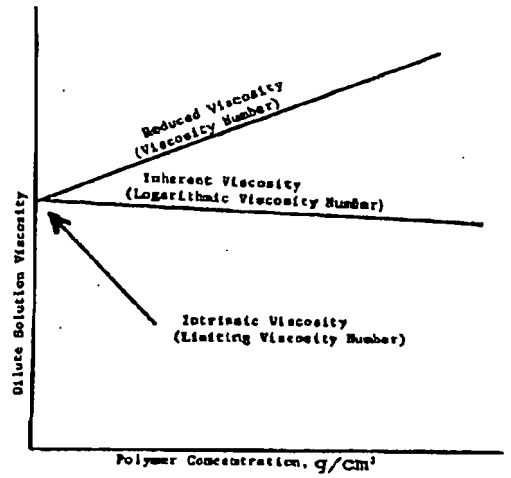

FIG. 1 Example of Plot to Determine Intrinsic Viscosity (Limiting Viscosity Number)

9.2 Add approximately 50 cm^3 of solvent to each specimen flask, purge with nitrogen if necessary, and shake on a laboratory shaker. Elevated temperature may enhance solution rate as suggested in Appendix X1, Practice D 5226, or specific test methods, but this approach should be used with caution. Some polymers and solvents have limited high-temperature stability. If solution preparation requires an elevated temperature, subject a flask of pure solvent to the same conditions as the polymer solution.

NOTE 8—**Caution:** Complete solution of all of the specimen is essential. When solution appears complete, examine the flask with care to be sure that no undissolved material, gel particles, or foreign matter is present.

9.3 Place the volumetric flasks containing the solution(s) and the pure solvent in the constant-temperature bath maintained at the test temperature. After temperature equilibrium has been achieved (10 to 30 min) complete the dilution to the 100-cm^3 mark by adding solvent maintained at the bath temperature, using a transfer pipet. Mix the contents of the flask(s) thoroughly.

NOTE 9—**Caution:** Be sure that the solution is uniformly mixed. If the test temperature is above ambient, avoid cooling the flask excessively while mixing.

9.4 Where necessary to prevent oxidation, purge the viscometer with a slow stream of nitrogen. With the viscometer permanently positioned in the constant-temperature bath at the required temperature, transfer a suitable amount of solution into the viscometer using a suitably modified transfer pipet (see 6.2). Pressure filtration through a fritted glass filter into the viscometer is often desirable, but care must be taken not to lose solvent during the process.

NOTE 10—If the solution is to be handled at elevated temperatures, the transfer pipet may be fitted with a suitable heating mantle to retard precipitation of polymer from the solution during the transfer.

9.5 After temperature equilibration has been achieved (a minimum of 10 min), bring the liquid level in the viscometer

[11] The Corning Glass No. 36060, or equivalent, has been found satisfactory for this purpose. The Corning Glass No. 36060 filter is available from Corning Glass Works, Corning, NY 14831.

[12] Available from Dow Corning Corp., Midland, MI; Union Carbide Corp., Linde Silicones Division, New York, NY; and General Electric Company, Silicone Products Dept., Waterford, NY.

[13] The Wiley mill, available from Scientific Supply houses, has been found satisfactory for this purpose.

above the upper graduation mark by means of gentle air (or, preferably, nitrogen) pressure or suction applied to the arm opposite the capillary. Allow the solution to drain down through the capillary. To measure the efflux time, start the timer exactly as the meniscus passes the upper graduation mark, and stop it exactly as the meniscus passes the lower mark.

NOTE 11—The use of automatic viscometers[14] can reduce the tedium and increase the precision of this step.

9.6 Determine the efflux time (see 9.5) at least three times each for the solution and for the pure solvent. Three consecutive readings should agree to within 0.1 s or 0.1 % of their mean, whichever is greater. Larger variations may result from foreign control in the viscometer or from inadequate temperature control, and require repetition of the experiment after their cause is located and corrected.

10. Calculation

10.1 *Relative Viscosity (Viscosity Ratio)*—Calculate the relative viscosity (viscosity ratio) from the average efflux time for the solvent, t_s, and the average efflux time for the solution, t, as follows:

$$\text{Relative Viscosity} = t/t_s$$

NOTE 12—Strictly, the relative viscosity (viscosity ratio) is defined as η/η_s where η and η_s are the viscosities of the solution and solvent, respectively, and are related to the corresponding efflux times by:

$$\eta = Ct\rho - E\rho/t^2$$

$$\eta_s = Ct_s\rho_s - E\rho_s/t_s^2$$

where:

C and E = constants for the particular viscometer used.

The equation in 10.1 follows if the second term in these relations, a kinetic-energy correction, is negligible and the respective solvent and solution densities, ρ_s and ρ, are substantially equal. This kinetic energy correction is negligible for the recommended viscometers and efflux times (see 4.4).[15]

10.2 *Inherent Viscosity (Logarithmic Viscosity Number)*—Calculate the inherent viscosity (logarithmic viscosity number) ratio for each solution concentration as follows:

$$\text{Inherent Viscosity} = \ln(\eta/\eta_s)/c$$

where:

$\ln(\eta/\eta_s)$ = the natural logarithm of the relative viscosity (viscosity ratio), and

c = the solution concentration in g/cm³ of solution.

The units of inherent viscosity (logarithmic viscosity number) are, therefore, cm³/g.

10.3 *Intrinsic Viscosity (Limiting Viscosity Number)*—Plot the inherent viscosity (logarithmic viscosity number) versus concentration, for several solution concentrations, on rectilinear graph paper as shown in Fig. 1. Draw the best straight line through the points and extrapolate it to zero concentration. The intrinsic viscosity (limiting viscosity number), $[\eta]$, is the intercept of the line at zero concentration. The units of the intrinsic viscosity (limiting viscosity number) are cm³/g.

NOTE 13—The reduced viscosity (viscosity number $(\eta - \eta_s)\eta_s c$) may be calculated and plotted versus concentration on the same graph with the inherent viscosity (logarithmic viscosity number). The two lines should extrapolate to the same point (the intrinsic viscosity or limiting viscosity number) at $c = 0$; plotting both functions may serve to fix the intrinsic viscosity (limiting viscosity number) with greater accuracy. If the limitation on relative viscosity (viscosity ratio) stated in Note 6 is observed, the extrapolation lines should be accurately straight.

NOTE 14—For some polymer-solvent systems, the slopes of the lines of reduced viscosity (viscosity number) and inherent viscosity (logarithmic viscosity number) versus concentration are closely similar for all samples normally encountered. For such systems, the intrinsic viscosity (limiting viscosity number) can be approximated from data obtained at a single concentration by one of the formulas tabulated by Billmeyer.[16]

11. Report

11.1 Report the following information:

11.1.1 Complete identification of the sample.

11.1.2 Conditioning procedure, if any.

11.1.3 One or more of the following:

11.1.3.1 The relative viscosity (viscosity ratio), given to one significant figure beyond the decimal point, followed by the concentration of the test solution in g/cm³.

11.1.3.2 The inherent viscosity (logarithmic viscosity number) in cm³/g, carried to one significant figure beyond the decimal point, followed by the concentration of the test solution in g/cm³.

11.1.3.3 The intrinsic viscosity (limiting viscosity number) in cm³/g, carried to the decimal point.

11.1.4 The solvent employed and the test temperature.

NOTE 15—ISO 1628/1 recommends a test temperature of 25 ± 0.05°C and use of kinetic energy corrections for some viscometers, so exercise caution when comparing data obtained by both test methods.

12. Precision and Bias

12.1 *Precision*—Based on test methods for vinyl chloride polymers in Test Method D 1243, and poly(ethylene terephthalate) in Test Method D 4603, within-laboratory repeatability of 1.5 to 2.0 % should be expected. Repeatability between laboratories ranged from 2.2 to 3.5 % for these same test methods.

12.2 *Bias*—Since viscosity numbers are available only from these measurements, there can be no estimate of bias.

13. Keywords

13.1 flow and flow rate—thermoplastics; polymers—molecular weight; viscosity—dilute-solution; viscosity—intrinsic; viscosity—plastics

[14] Suitable automatic viscometer equipment is available from Cannon Instruments, State College, PA, and Schott America, Yonkers, NY.

[15] Cannon, M. R., Manning, R. E., and Bell, J. D., "Viscosity Measurement: The Kinetic Energy Correction and a New Viscometer," *Analytical Chemistry*, Vol 32, 1960, pp. 355–358.

[16] Billmeyer, F. W., Jr., "Methods for Estimating Intrinsic Viscosity," *Journal of Polymer Science*, Vol 4, 1949, pp. 83–86.

APPENDIX

(Nonmandatory Information)

X1. RECOMMENDED SOLVENTS AND SOLUTION CONCENTRATIONS

X1.1 Polyamide (in accordance with Test Methods D 789)

X1.1.1 The recommended solution concentration is 0.0050 ± 0.00002 g/cm^3.

X1.1.2 The recommended dissolving conditions are: for formic acid (90 ± 0.2 % in water), 30°C; for *m*-cresol (11 to 12°C melting point), 95 to 100°C (2-h maximum), or 8 h at 50°C.

X1.1.3 The recommended test temperature is 30°C.

X1.2 Polycarbonate

X1.2.1 The recommended solution concentration is 0.0040 ± 0.0002 g/cm^3, or by convenient dilution from 0.010 ± 0.00002 g/cm^3.

X1.2.2 The recommended dissolving conditions are: for methylene chloride, 30°C, or for *p*-dioxane (dry), 60°C.

X1.2.3 The recommended test temperature is 30°C.

X1.2.4 If pigments or other fillers are present, the resin may be dissolved in methylene chloride and the solution filtered. The methylene chloride may be evaporated from the resulting clear solution to leave the resin in the form of a thin film which may be sampled for viscosity measurements after drying several hours at 125°C.

X1.3 Poly(Methyl Methacrylate)

X1.3.1 The recommended solution concentration is 0.0020 ± 0.00002 g/cm^3; but the recommendation of Note 5 should be understood to supersede this.

X1.3.2 The recommended dissolving conditions are 30°C for 24 h in 1,2-dichloroethane (ethylene dichloride).

X1.3.3 The recommended test temperature is 30°C.

X1.3.4 Pretreatment of the sample should not include cutting or grinding in such a way as to cause shear degradation of the polymer.

X1.4 Poly(Vinyl Chloride) (in accordance with Test Method D 1243)

X1.4.1 The recommended solution concentration is 0.2 ± 0.002 g/100 cm^3.

X1.4.2 The recommended dissolving conditions include 12 h at 85 ± 10°C in cyclohexanone.

X1.4.3 The recommended test temperature is 30°C.

The American Society for Testing and Materials takes no position respecting the validity of any patent rights asserted in connection with any item mentioned in this standard. Users of this standard are expressly advised that determination of the validity of any such patent rights, and the risk of infringement of such rights, are entirely their own responsibility.

This standard is subject to revision at any time by the responsible technical committee and must be reviewed every five years and if not revised, either reapproved or withdrawn. Your comments are invited either for revision of this standard or for additional standards and should be addressed to ASTM Headquarters. Your comments will receive careful consideration at a meeting of the responsible technical committee, which you may attend. If you feel that your comments have not received a fair hearing you should make your views known to the ASTM Committee on Standards, 1916 Race St., Philadelphia, PA 19103.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
59098WO003		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2004/040707	03/12/2004	05/12/2003
Applicant		
3M INNOVATIVE PROPERTIES COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/040707

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/040707

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/58 A61L15/42 A61L15/22 A61L15/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/066087 A (COLOPLAST A/S; LYKKE, MADS) 29 August 2002 (2002-08-29) page 9, line 1 - page 10, line 7 page 11, line 11 - line 20 example 2 claims	1-23
P,X	WO 2004/080498 A (3M INNOVATIVE PROPERTIES COMPANY; HYDE, PATRICK, D; MENZIES, ROBERT, H) 23 September 2004 (2004-09-23) page 22, line 1 - line 24 tables 1,3,7,9 examples claims	1-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2005	11/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Thornton, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/040707

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/080499 A (3M INNOVATIVE PROPERTIES COMPANY; BURTON, SCOTT, A; HYDE, PATRICK, D) 23 September 2004 (2004-09-23) page 17, line 23 - page 19, line 2 claims examples	1-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/040707

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02066087 A	29-08-2002	CA 2438875 A1	29-08-2002
		CN 1492770 A	28-04-2004
		WO 02066087 A1	29-08-2002
		EP 1361904 A1	19-11-2003
		HU 0303168 A2	29-12-2003
		JP 2004527600 T	09-09-2004
		US 2004065232 A1	08-04-2004
WO 2004080498 A	23-09-2004	WO 2004080498 A1	23-09-2004
WO 2004080499 A	23-09-2004	US 2004180093 A1	16-09-2004
		WO 2004080499 A1	23-09-2004

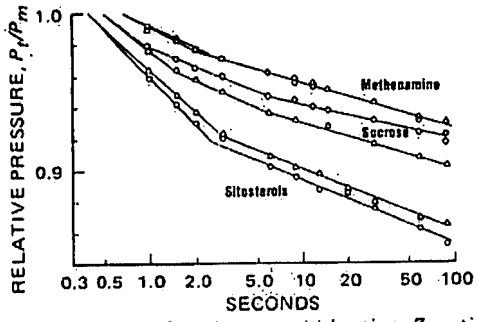

Figure 21—*Relative punch pressure versus log time. Zero time corresponds to the start of stress application. Circles and diamonds are data from an in air measurement; triangles are data from an* in vacuo *measurement. Only material with the slowest rate of relaxation fractured upon rapid decompression in the die. Maximum pressures (in $N/m^2 \times 10^{-7}$) were: methenamine, air 8.34 and* in vacuo *8.41; sucrose, air 6.96 and* in vacuo *6.52; and sitosterols, air 4.62 and* in vacuo *4.07.*

The time-dependent nature of plastic flow or stress relaxation also must be considered and may account for differences in the properties of tablets produced on various machines or at various machine settings.

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[x] To whom inquiries should be directed.

Solubility Studies of Silver Sulfadiazine

R. U. NESBITT, Jr. [*], and B. J. SANDMANN [x]

Abstract □ The solubility of silver sulfadiazine as a function of pH was determined in nitric acid–potassium nitrate buffer for pH 2–3 and in 2-(*N*-morpholino)ethanesulfonic acid buffer for pH 6–7. As the salt of a weak organic acid, silver sulfadiazine exhibits the anticipated increase in solubility with an increasing hydrogen-ion concentration. Measurement of the silver-ion concentration was carried out using a silver-ion selective electrode. The methods of known subtraction and known addition were utilized to measure the total concentration of the silver ion in solution. Evidence was obtained to indicate that the salt is completely ionized in aqueous solution.

Keyphrases □ Silver sulfadiazine—solubility as a function of pH, potentiometric study □ Solubility—silver sulfadiazine as a function of pH, potentiometric study □ pH—effect on solubility of silver sulfadiazine, potentiometric study □ Potentiometry—study of solubility of silver sulfadiazine as a function of pH □ Anti-infectives, topical—silver sulfadiazine, solubility as a function of pH, potentiometric study

Silver sulfadiazine, a substance with extremely low water solubility, was reported to be particularly efficacious as a topical antibacterial agent for the control of *Pseudomonas* infection in burns (1). When applied locally to burned skin, silver sulfadiazine is claimed to offer definite therapeutic advantages over other similar chemotherapeutic agents used to treat infection. Unlike other drugs that diffuse rapidly or deplete chloride ions from body fluids, silver sulfadiazine remains in the wound exudate for a prolonged effect and appears to enhance conditions favorable for epithelial regeneration.

BACKGROUND

The mode of antibacterial action is different than that of sulfonamides; because the drug is not antagonized *in vitro* by aminobenzoic acid. In binding studies using radioactive silver sulfadiazine prepared from radioactive ^{110}Ag- and ^{35}S-tracers, the silver ion was found to bind with the *Pseudomonas* cells. No cellular binding of sulfadiazine was detected (2, 3).

The binding of silver to bacterial DNA was proposed as important for inhibiting microbial growth. Silver displaces the hydrogen bonds between adjacent nitrogens of the purines (adenine or guanine) and pyrimidines (thymine and cytosine) in the DNA molecule. The nitrogen–silver bonds, once formed, appear to be stronger than the nitrogen–hydrogen bonds; therefore, bacteria having this silver–nucleic acid complex presumably

do not replicate (4). In another report, silver sulfadiazine was said to bind to cell membranes rather than to interact with cellular DNA (5).

The mechanism of action of silver sulfadiazine is incompletely defined, and the exact role of the sulfadiazine moiety remains unclear. One proposal suggests that sulfadiazine localizes the action of the drug to the microbial cells (2). The very slow reaction of silver sulfadiazine with endogenous chloride ions is interesting when enough silver ions are apparently present to produce a strong antibacterial effect, but silver chloride reportedly does not precipitate in tissue fluids. The dissociation of silver sulfadiazine during inhibition of bacterial growth was described (3) in contrast to an earlier report that silver sulfadiazine does not ionize (6). Additional studies to determine the solubility and ionization properties of silver sulfadiazine are necessary for a complete understanding of its mechanism of action.

The crystallization and structure of silver sulfadiazine were recently reported, and the drug was characterized as a salt of a weak acid (7). A study using X-ray diffraction confirmed the assigned structure (8). The current report is concerned with the behavior of silver sulfadiazine in aqueous solutions in the presence of electrolytes and buffers. The objectives of this study were to investigate the ionization and solubility of silver sulfadiazine using recently developed potentiometric methods and to relate these properties with those of the silver salts of other N^1-substituted sulfonamides.

EXPERIMENTAL

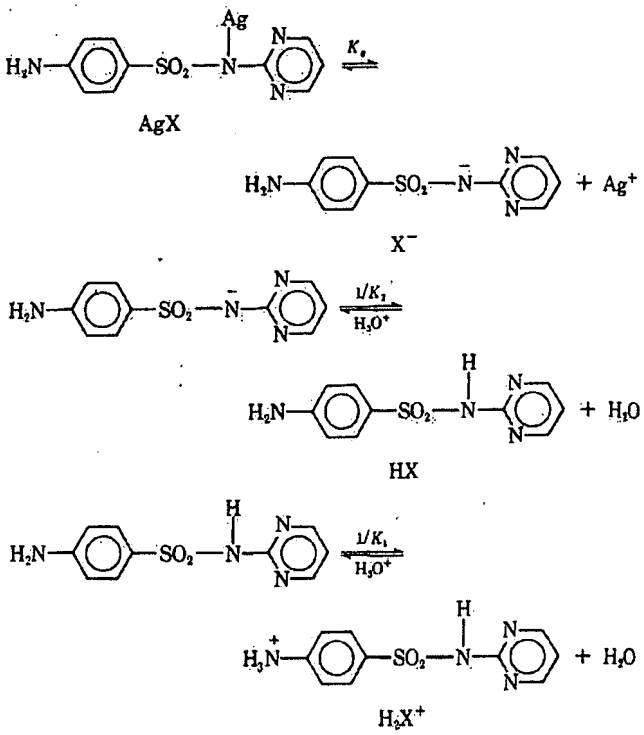
Equipment—Potentiometric measurements were made using a pH meter[1], accurate to ±0.1 mv or ±0.001 pH unit, in a thermostated bath regulated at 25 ± 0.1°. The silver-ion concentration was measured with a silver-ion selective electrode[2]. The hydronium-ion concentration was measured with a triple-purpose pH electrode[3]. A double-junction silver chloride reference electrode[4] with a filling solution of 10% KNO_3 was used to eliminate the possible precipitation of silver chloride in the sample solutions.

Reagents—All reagents were of analytical grade, unless otherwise stated. Water with a specific conductivity of 1–10 × 10^{-7} ohm^{-1} cm^{-1} was employed. Silver nitrate[5] and sodium sulfadiazine[5] were obtained commercially. Silver sulfadiazine was prepared by the method of Braun and Towle (9) and recrystallized as previously described (7). The 2-(*N*-morpholino)ethanesulfonic acid buffer[6] was prepared by titration of the acid with a standard sodium hydroxide solution.

Preparation of Equilibrium Mixtures—Silver sulfadiazine was screened through a size 80 standard screen[7]. Paraffin-coated vials with film-covered[8] rubber closures held in place by aluminum bands were utilized. Mixtures of 100 mg of silver sulfadiazine, 25 ml of nitric acid buffer, or 25 ml of 0.05 *M* 2-(*N*-morpholino)ethanesulfonic acid buffer were prepared, adjusted to an ionic strength of 0.1 *M* with potassium nitrate, and placed in the coated vials. For the measurement of total silver, 27 ml of buffer solution was used. The vials were rotated end-over-end in the thermostated bath until equilibrium solubility was obtained.

Measurement of Silver—After filtration of the equilibrated mixtures, the solutions were analyzed at 25 ± 0.1° in paraffin-coated beakers for the silver-ion concentration using a silver-ion selective electrode[2] standardized at 25 ± 0.1° and an ionic strength of 0.1 *M*. The electrode displayed a Nerstian response throughout the concentration range of 1 × 10^{-2}–1.5 × 10^{-6} *M* for the silver ion. The pH was measured with a pH electrode[3] standardized using standard buffers meeting National Bureau of Standards requirements (10). The total silver concentration was determined by the method of known subtraction (11, 12) in the nitric acid-buffered solution, to which a sufficient amount of a standard solution of potassium iodide was added to precipitate approximately one-half of the free silver ion. In the 2-(*N*-morpholino)ethanesulfonic acid-buffered solutions, the total silver concentration was determined by the method of known addition (12); the added reagent was a standard solution of silver nitrate representing a 100-fold increase in the free silver ion present in the sample solutions.

[1] Corning digital 112 research pH meter, Corning Scientific Instruments, Medfield, Mass.
[2] No. 94-16, Orion Research, Cambridge, Mass.
[3] Corning Scientific Instruments, Medfield, Mass.
[4] No. 90-02, Orion Research, Cambridge, Mass.
[5] Marion Laboratories, Kansas City, Mo.
[6] United States Biochemical Corp., Cleveland, Ohio.
[7] W. S. Tyler Co., Minton, Ohio.
[8] Parafilm, American Can Co., Neenah, Wis.



Scheme I

RESULTS AND DISCUSSION

In aqueous solutions, silver sulfadiazine would be expected to exhibit the general properties of the salt of a weak acid. The measurement of these properties, however, presents an analytical problem due to its extremely low water solubility. The recent development of ion selective electrode technology along with two new techniques for measuring total ion concentrations suggested the application of a potentiometric method for the analysis of silver sulfadiazine. In distilled water, the solubility of silver sulfadiazine is below the limits of analysis by any potentiometric method. However, in dilute acid, enough silver ions are ionized to give a concentration well within the sensitivity of a silver-ion specific electrode. Hydrolysis of the silver ion at near neutral or alkaline pH limits the study of silver sulfadiazine solubility to pH values less than 7.

The tendency of the silver ion to complex with various molecules and other ions reduced the number of possible buffering agents. Of the common inorganic salts of strong electrolytes, only nitrate and perchlorate ions remain in solution in the presence of silver ions. Nitric acid–potassium nitrate buffers were employed over a limited pH range. A suitable buffer for silver ions in the pH 6–7 range has not been identified. The sulfonic acid buffer system chosen exhibits minimal complexation with the silver ion (13). The use of conditional solubility product constants permits limited conclusions on solubility at this pH range.

Saturated solutions of silver sulfadiazine were analyzed for free and total silver concentrations by the analytical techniques of known addition (12) and known subtraction (11, 12). These methods were necessary due to the high probability of complexation of the silver with the sulfonic acid buffer as well as the uncertainty of the ionization properties of silver sulfadiazine. With nitrate buffers, the known subtraction method was utilized to determine the extent of ionization of the silver ion from the sulfadiazine. With this method, a complexing agent that will completely precipitate about one-half of the ion measured is added to the sample and the observed change in potential is used to calculate the original total ion concentration. By measuring the activity of free ion by a direct measurement using a calibration curve, it is possible to calculate the amount undissociated.

Due to the complexation of silver with the sulfonic acid buffer, the known addition method was used wherein a known solution of the ion being measured is added to the sample of interest. The original ion concentration is then calculated from the observed increase in potential. The usefulness of these methods depends on how well the system obeys the inherent assumptions.

The equilibria of the saturated solutions depicted by Scheme I may

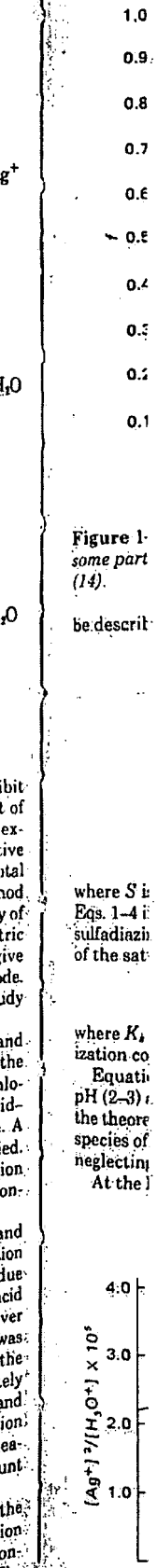


Figure 1· *some part (14).*

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where *S* i Eqs. 1–4 i sulfadiazi of the sat

where K_s ization co Equati pH (2–3) the theore species of neglectin At the

Figure 2· *0.1 M ion*

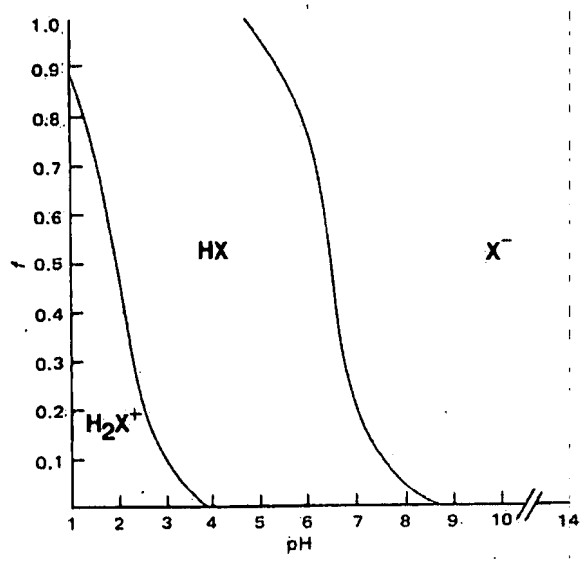

Figure 1—*Distribution diagram: fraction of sulfadiazine present as some particular form, f, as a function of pH; $pK_1 = 2.09$, and $pK_2 = 6.45$ (14).*

be described by:

$$K_s = [Ag^+][X^-] \quad \text{(Eq. 1)}$$

$$\frac{1}{K_2} = \frac{[HX]}{[H_3O^+][X^-]} \quad \text{(Eq. 2)}$$

$$\frac{1}{K_1} = \frac{[H_2X^+]}{[HX][H_3O^+]} \quad \text{(Eq. 3)}$$

$$S = [Ag^+] \quad \text{(Eq. 4)}$$

$$S = [H_2X^+] + [HX] + [X^-] \quad \text{(Eq. 5)}$$

where S is the total molar solubility of silver sulfadiazine. Substituting Eqs. 1–4 into Eq. 5 gives an equation that describes the solubility of silver sulfadiazine in terms of only the silver- and hydronium-ion concentrations of the saturated solution:

$$S^2 = [Ag^+]^2 = \frac{[H_3O^+]^2K_s}{K_1K_2} + \frac{[H_3O^+]K_s}{K_2} + K_s \quad \text{(Eq. 6)}$$

where K_s is the solubility product constant, and K_1 and K_2 are the ionization constants of the N^4- and N^1-hydrogens, respectively.

Equation 6 may be simplified by using the limiting conditions of low pH (2–3) and high pH (6–7). These approximations were derived by using the theoretical distribution diagram for sulfadiazine (Fig. 1), noting which species of sulfadiazine were not present in the pH range of interest, and neglecting this term in the mass balance (Eq. 5).

At the low pH range, Eq. 6 may be approximated to give:

$$S^2 = [Ag^+]^2 = \frac{[H_3O^+]^2K_s}{K_1K_2} + \frac{[H_3O^+]K_s}{K_2} \quad \text{(Eq. 7)}$$

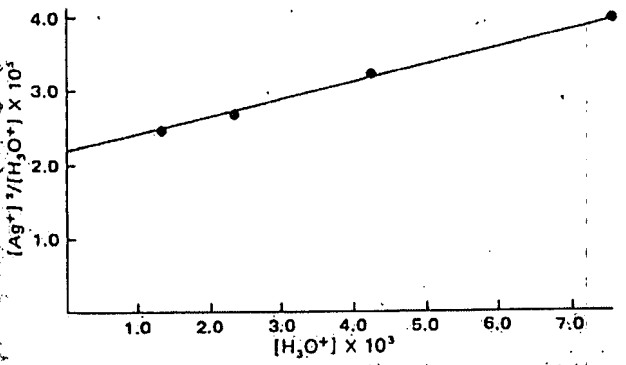

Figure 2—*Equilibrium values of $[Ag^+]^2/[H_3O^+]$ versus $[H_3O^+]$ at 0.1 M ionic strength and 25 ± 0.1°.*

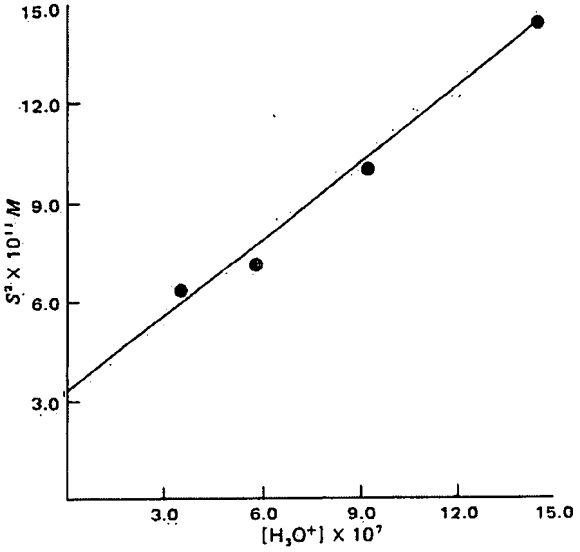

Figure 3—*Equilibrium values of S^2 versus $[H_3O^+]$ in 0.05 M 2-(N-morpholino)ethanesulfonic acid buffer at 0.1 M ionic strength and 25 ± 0.1°.*

by neglecting the X^- species in Eq. 5. This equation may be linearized by dividing both sides by the hydronium-ion concentration, giving Eq. 8:

$$\frac{[Ag^+]^2}{[H_3O^+]} = \frac{[H_3O^+]K_s}{K_1K_2} + \frac{K_s}{K_2} \quad \text{(Eq. 8)}$$

When $[Ag^+]^2/[H_3O^+]$ is plotted against $[H_3O^+]$, a linear relationship should exist with an intercept of K_s/K_2 and a slope of $K_s/K_2(1/K_1)$. From the slope and intercept, K_1 may be experimentally determined under the given conditions.

In the pH range of 6–7, Eq. 6 may be approximated to give:

$$S^2 = [Ag^+]^2 = \frac{[H_3O^+]K_s}{K_2} + K_s \quad \text{(Eq. 9)}$$

where the H_2X^+ species in Eq. 5 has been neglected. The application of Eq. 9 to the experimental data in the presence of the 2-(*N*-morpholino)-ethanesulfonic acid buffer does not completely represent the system due to apparent complexation of the free silver ion with the buffer, giving an increased value of the solubility, S, and subsequently a higher value for K_s, the solubility product constant.

A suitable modification of Eq. 9 to include this complexation may be made by using a conditional solubility product constant, K_s', defined by:

$$K_s' = [Ag^+]'[X^-] \quad \text{(Eq. 10)}$$

where $[Ag^+]'$ represents the concentration of all silver in solution irrespective of the form in which the silver ion may be present. Equation 9 may now be rewritten as:

$$S^2 = \frac{[H_3O^+]K_s'}{K_2} + K_s' \quad \text{(Eq. 11)}$$

Table I—Comparison of Total Molar Solubility, S, of Silver Sulfadiazine Determined by the Method of Known Subtraction with the Molar Concentration of the Silver Ion Determined by Direct Potentiometry on Identical Samples at 25 ± 0.1°, Ionic Strength 0.1 M, in Nitric Acid Buffers

	pH 2.128		pH 3.851	
	$S \times 10^5$	$[Ag^+] \times 10^5$	$S \times 10^5$	$[Ag^+] \times 10^5$
	59.18	59.11	6.690	6.455
	58.06	57.97	6.690	6.517
	59.35	59.34	6.434	6.517
	58.53	58.42	6.768	6.475
	59.19	60.00	6.586	6.375
	57.30	57.97	6.612	6.455
Mean	58.60	58.80	6.466	6.629

Table II—Calculation of Solubility Product of Silver Sulfadiazine Using Eq. 13 at 25 ± 0.1° and Ionic Strength 0.1 *M*

pH	f_0[a]	$[Ag^+]^2$	K_s
2.122	2.688×10^{-1}	2.980×10^{-7}	8.04×10^{-12}
2.373	6.024×10^{-1}	1.352×10^{-7}	8.16×10^{-12}
2.630	1.279×10^{-1}	6.165×10^{-8}	7.90×10^{-12}
2.891	2.583×10^{-1}	3.139×10^{-8}	8.14×10^{-12}
Mean	$8.06 \times 10^{-12} \pm 0.12$		

[a] $K_1 = 8.59 \times 10^{-3}$, and $K_2 = 3.82 \times 10^{-7}$.

where S is the total molar solubility, and K_2 is defined by Eq. 2. A plot of S^2 *versus* $[H_3O^+]$ would be expected to be linear with an intercept of K_s' and a slope of K_s'/K_2, from which K_2 may be experimentally determined.

Figure 2 is a linear plot of the equilibrium values of $[Ag^+]^2/[H_3O^+]$ against the equilibrium $[H_3O^+]$ value, having a slope of 2.459×10^{-3} and an intercept of 2.112×10^{-5}. From the slope and intercept, pK_1 was found to be 2.07 ± 0.06 at an ionic strength of 0.1 *M*. This value is in agreement with a literature value of 2.09 (14). As shown in Fig. 3, a plot of S^2 *versus* $[H_3O^+]$ at equilibrium is linear with an intercept of 3.05×10^{-11} and a slope of 7.98×10^{-5}. From the slope and intercept, pK_2 was evaluated experimentally to be 6.42 ± 0.04, in agreement with a previously reported value of 6.45 (14).

The possibility of intact silver sulfadiazine in solution in a pH range of 2.1–3.8 was investigated by comparison of the total molar solubility, S, as determined by the method of known subtraction, with the molar concentration of free silver ion, $[Ag^+]$, by direct potentiometric analysis on identical samples under the given experimental conditions. By the use of one-way analysis of variance, the means displayed in Table I are not statistically different at the 5% level. Therefore, in the pH 2–3 range,

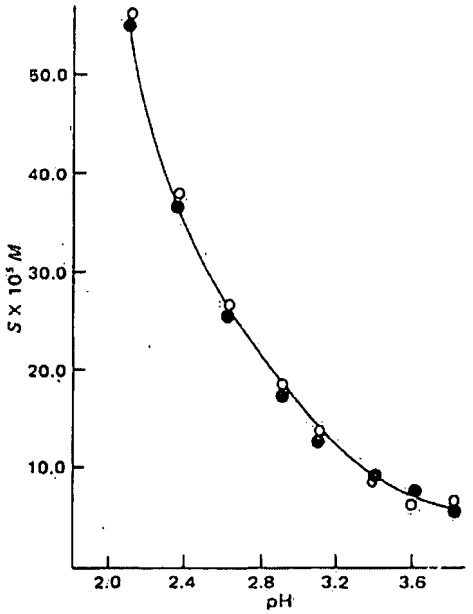

Figure 4—*Molar solubility (S) of silver sulfadiazine* versus *pH at 0.1 M ionic strength and 25 ± 0.1°. Key:* ●, *experimental values; and* ○, *calculated from Eq. 7 and the equilibrium constants determined in this study.*

the solubility, S, of silver sulfadiazine is given by Eqs. 4 and 5. The solubility product of silver sulfadiazine is given by Eq. 1. By substituting Eqs. 2 and 3 into Eq. 5, an expression may be derived giving the ratio, f_0, of the sulfadiazine anion to the total solubility, where:

$$f_0 = \frac{[X^-]}{S} = \left(1 + \frac{[H_3O^+]}{K_2} + \frac{[H_3O^+]^2}{K_1K_2}\right)^{-1} \quad \text{(Eq. 12)}$$

Combining this expression with Eq. 1 gives:

$$K_s = f_0S^2 \quad \text{(Eq. 13)}$$

Application of this equation to the experimental data at the low pH range is given in Table II, where the mean solubility product constant for silver sulfadiazine was $8.06 \pm 0.12 \times 10^{-12}$.

A plot of the molar solubility, S, of silver sulfadiazine against pH over the pH range studied is displayed in Fig. 4. This plot at pH 2–3 compares very closely with the distribution of the sulfadiazine cation over the same pH range. Thus, the solubility of silver sulfadiazine is directly a function of sulfadiazine ionization.

The solubility would be expected to be nearly pH independent in the pH 4–5 range where the predominant sulfadiazine species is the neutral molecule. For pH 6–7, the solubility is estimated by Eq. 9. At pH 6, the calculated solubility, S, was 5.40×10^{-6} *M*; at pH 7, it was 3.19×10^{-6} *M*. Where the predominant sulfadiazine species is the sulfadiazine anion, the limiting value of the solubility would be expected to be the square root of the solubility product constant, $\sqrt{K_s} = 2.83 \times 10^{-6}$ *M*.

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